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Summary Review of Health Effects Associated with Hydrogen Fluoride and Related Compounds

Health Issue Assessment

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Health Issue Assessment

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

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This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Preface

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of hydrogen fluoride as a hazardous air pollutant.

In the development of this assessment document, the scientific literature through January 1987 has been inventoried, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available exposure information is presented as accurately as possible, it is acknowledged to be limited and dependent in some instances on assumption rather than specific data. This exposure information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, a considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

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1. Summary and Conclusions

Anhydrous hydrogen fluoride (HF) is a colorless, fuming corrosive liquid or gas at room temperature and is one of the strongest acids known; aqueous HF, or hydrofluoric acid, is a weak acid. Hydrogen fluoride is highly reactive with a number of materials. Some HF is produced naturally by volcanic activity; commercial production is by the reaction of sulfuric acid with fluorspar. Hydrogen fluoride is probably the most important of the many fluorine-containing compounds, because it is used in the production of most of the other fluorine compounds.

The major uses of hydrogen fluoride are in the aluminum and fluorocarbon industries. Steel production is a major user of solid inorganic fluoride (F^-) in the form of fluorspar. Hydrogen fluoride and other inorganic fluoride compounds are also important for a number of other uses (e.g., uranium processing, petroleum alkylation, manufacturing fluoride salts, and metal pickling and fluxing operations). Total HF and fluorspar consumption has decreased since 1974, and an increasing proportion of the HF and fluorspar used in the United States is imported.

The major natural sources of airborne HF and other airborne fluorides are volcanic activity, ocean spray, and dust from the weathering of fluoride-containing rocks or soils. Anthropogenic sources include emissions from industrial operations consuming HF or fluorspar and from the combustion of coal for power; these sources may contribute as much as 150 thousand metric tons of airborne fluoride per year in the United States and 3.6 million metric tons per year worldwide. Twenty to forty percent of industrial fluoride emissions are in gaseous form, the rest are particulate. Many of the gaseous fluorides, including HF, are hydrolyzed and dispersed in the atmosphere; particulate fluorides generally settle to the ground as dusts. The major route for removal of airborne fluoride is atmospheric precipitation, and most of the fluoride in precipitation is thought to be of anthropogenic origin.

At least 300,000 workers in the United States may have potential exposure to HF or to other inorganic fluorides. Occupational HF and fluoride (as F) exposure limits are set at 2.5 mg/m^3 (3 ppm HF) for an 8-hour working day. A maximum of 10 to 25 mg fluoride per day could be inhaled by a worker under these exposure limits. Exposure of the general public to airborne fluorides, including HF, is greatest in the vicinity of point sources such as factories; average total fluoride concentrations near industrial operations in the United States and Canada are normally below 8.2 $\mu g/m^3$. People living in highly polluted industrial areas probably inhale at most 0.2 mg of fluoride per day. Fluoride intake from food and water is probably about 2 to 3 mg/day (normal range, 0.25 to 5.4 mg/day) per person, depending on individual diet and whether or not the local water supply is fluoridated. Cigarette smokers may inhale as much as 0.8 mg fluoride per day. Fluoride intake may also occur from other sources such as fluoridated dentifrices. Most of the toxic effects of hydrogen fluoride to humans are attributable to the fluoride ion, and fluoride exposure from all sources must be assessed in the determination of the health effects of HF or fluoride on the human population.

Absorption of fluoride in mammals is dependent primarily on the solubility of the specific compound: NaF is readily absorbed in the gastrointestinal tract, CaF_2 much less so. Hydrogen fluoride is rapidly absorbed via the lungs, skin, or gastrointestinal tract. Not all particulate fluorides are actually deposited in or absorbed from the respiratory tract; some are exhaled without ever being deposited on the surface of the respiratory tract. As much as one half of absorbed fluoride may be retained in the human body, most of it in the skeleton. The plasma concentration of ionic fluoride is directly related to the fluoride content of the drinking water and is normally in the range of 10 to 20 µg/L. Clearance from the blood is by uptake into bones or teeth (especially in children), where it replaces hydroxyl ions in the apatite lattice, and by excretion via the kidneys. Urinary excretion is the main route of removal of fluoride from the body, and fluoride levels in urine are correlated with fluoride intake. People with renal dysfunction will excrete less than normal amounts of fluoride; because of the increased retention of fluoride, these people are at a higher risk for toxic effects caused by fluoride.

Some studies have suggested that HF and NaF are genotoxic in plants, *Drosophila*, or mammals, primarily by causing chromosome breakage. The fluoride concentrations used to induce genotoxic effects in many *in vivo* experiments are several hundred to several thousand times higher than the blood fluoride levels expected in humans. Epidemiological studies have not provided evidence for an association between fluoride in drinking water and an increased risk of cancer mortality. Increased rates of cancer have been reported for workers in several occupations involving possible fluoride exposure; however, all these situations involved mixed exposures to several chemicals, and fluoride could not be specifically implicated as the cause of the cancers. No animal bioassays have been reported on the potential carcinogenicity of inhaled fluorides, and tests of sodium fluoride administered orally to mice have been inconclusive. The available evidence is thought to be inadequate to support or refute a carcinogenic potential for inhalation exposure to fluorides. The United States Environmental Protection Agency has not classified fluoride or hydrogen fluoride with respect to potential carcinogenicity.

Fluoride can cross the placenta and be deposited in the calcified tissues of the fetus; fetal exposure is proportional to maternal exposure. High levels of fluoride have caused impaired reproduction or malformation of fetal bones and teeth in some mammalian species, but no adverse effects on human reproduction or fetal development are expected at fluoride levels likely to be encountered by humans.

The major developmental risk to humans from fluoride is dental mottling or fluorosis. This occurs in individuals receiving excess fluoride (usually in the drinking water) during the period of tooth mineralization (prior to birth for deciduous teeth and up to age 12 for the last of the permanent teeth). Mild to moderate dental fluorosis (from water fluoride levels up to 4 mg/L) is considered a cosmetic effect rather than a health effect.

Acute exposure to gaseous fluoride is rare in a nonoccupational setting. Hydrogen fluoride and fluorine are extremely toxic, with IDLH ("immediately dangerous to life and health") levels of 16.4 and 50 mg/m^3 (20 and 25 ppm), respectively. Both gases can cause severe respiratory damage or skin burns on contact. Aqueous hydrofluoric acid also causes severe burns. The skin burns and respiratory damage caused by hydrogen fluoride are the only toxic effects of hydrogen fluoride which are not attributable solely to the action of the fluoride ion, and systemic fluoride poisoning usually does occur from HF absorbed via the lungs or the skin. Ingested fluorides also cause systemic

fluoride poisoning. Symptoms of acute fluoride poisoning include convulsions and cardiac arrhythmias, and death is usually from cardiac or respiratory failure and occurs within 24 hours. An acute dose of 8 to 16 mg fluoride per kg body weight can be safely tolerated by humans; a dose of 32 to 64 mg/kg is lethal. No acute effects of hydrogen fluoride or other inorganic fluorides are noticed at air fluoride levels of 2.6 mg/m^3.

The bones and teeth are the tissues most sensitive to long-term fluoride intake. Chronic fluoride exposure to 0.1 to 0.35 mg/kg/day during childhood can result in dental fluorosis or mottling. Skeletal fluorosis requires a higher fluoride intake (0.2 to 1.0 mg/kg/day or more) over many more years. The earliest observable effect of fluoride deposition in the skeleton is an increased opacity of the bone to X-rays, known as osteosclerosis, which is first noticeable when the fluoride level reaches 5000 to 6000 mg/kg of dry, fat-free bone. Skeletal fluorosis increases in severity with increased fluoride intake and increased time. Crippling fluorosis is characterized by pain, stiffness, irregular bone growth, and calcification of ligaments and tendons; this occurs only when occupational fluoride exposure has been very high (resulting in an intake of 20 to 80 mg/day for 10 to 20 years) or when drinking water contains 10 to 40 mg/L fluoride. Other effects of chronic fluoride exposure on humans have been reported, including hypersensitivity and dermatological reactions, but none has been convincingly established. The United States Environmental Protection Agency (1986) has established an oral Reference Dose (RfD) of 0.06 mg/kg/day for children (corresponding to a water fluoride level of 1 mg/L) which is adequate to prevent dental and skeletal fluorosis. An inhalation RfD is not available.

Fluoride toxicity involves at least four major effects: inhibition of various enzymes, hypocalcemia, cardiovascular collapse, and damage to specific organs such as the brain and the kidneys. The major chronic effects of fluoride may be caused by the action of the fluoride ion on various enzymes and thereby on metabolic pathways. Many of the acute toxic effects of fluoride, such as the cardiac arrhythmias, may be caused by hypocalcemia, and most methods of treatment of acute fluoride poisoning or HF burns include immediate replacement of calcium.

It is generally accepted that fluoride has a significant cariostatic effect on human teeth, particularly for individuals who receive it during childhood. Fluoride acts systemically in the formation of teeth by being built into the crystal structure of the enamel, making it harder and more resistant to decay; fluoride also acts topically on erupted teeth by promoting remineralization and by inhibiting acid production by bacteria. In many communities, fluoride is administered to the population via the water supply, typically at a level of 1 ppm fluoride, depending on the average local temperature. A few reports suggest that at least some of the decline in tooth decay attributed to fluoridated water may in fact be due to other causes, such as changes in immune status, changes in dietary patterns, and use of topical fluorides.

The use of fluoride has also been suggested as a means of preventing or treating osteoporosis, or premature bone loss. Some evidence exists which indicates that people living in an area with a high natural level of fluoride in the water (4 to 8 mg/L) have a lower incidence of osteoporosis, but medical use of high fluoride doses is still under investigation. Fluoridated water may also be correlated with a lower incidence of cardiovascular disease. The beneficial effects and the adverse effects of fluoride must be weighed in determining the optimal dose for humans, and in particular for the optimal fluoride level to be maintained in public water supplies.

In summary, most of the toxic effects of hydrogen fluoride are attributable to the effects of fluoride ion. Acute inhalation of HF or skin contact with HF or hydrofluoric acid results in respiratory damage or skin burns, as well as systemic fluoride effects. Average air fluoride concentrations near industrial operations are usually less than 8.2 $\mu g/m^3$ and exposure of the general public to airborne fluorides is normally less than 0.2 mg/day per person in industrial areas and even less in rural areas. For most people, exposure to airborne fluorides is considerably less than exposure to fluoride from other sources such as food and water; nevertheless exposure to fluoride from all sources must be assessed in the accurate determination of the health effects on the human population. Most people probably ingest 0.25 to 5.4 mg fluoride per day, depending on individual diet and the fluoride content of local water supplies; smokers may inhale another 0.8 mg fluoride per day. Table 1-1 contains a summary of human fluoride intake from various sources.

Some fluoride intake, about 0.06 mg/kg/day (1.2 mg/day in a 20-kg child or 4.2 mg/day in a 70-kg adult) has a beneficial effect in the prevention of dental caries, particularly for those receiving it during childhood. A fluoride intake of 0.2 to 0.35 mg/kg/day (4 to 7 mg/day for a child) during childhood commonly causes dental fluorosis. Long-term fluoride intake of 0.2 to 1.0 mg/kg/day (14 to 70 mg/day for an adult) or more will result in severe skeletal fluorosis. An acute fluoride intake of 8 to 16 mg/kg can be safely tolerated by humans; a dose of 32 to 64 mg/kg is lethal. Table 1-2 summarizes the effects on humans of various levels of fluoride intake, and Table 1-3 summarizes the existing official standards and human toxicity limits for airborne hydrogen fluoride, fluorine, and inorganic compounds of fluoride.

Table 1-1. Summary of Human Fluoride Intake from Various Sources

Source	Fluoride Intake[a]			
	20 kg child		70 kg adult	
	mg/kg/day	mg/day	mg/kg/day	mg/day
Food	0.01	0.2	0.01	0.7
Drinking water				
1 ppm fluoride	0.05	1.0	0.03	2.0
2 ppm fluoride	0.10	2.0	0.06	4.0
4 ppm fluoride	0.20	4.0	0.11	8.0
8 ppm fluoride	0.40	8.0	0.23	16.0
10 ppm fluoride	0.50	10.0	0.29	20.0
Fluoridated dentifrices and mouthwashes	0.013	0.25	0.004	0.25
Air[b]				
2 g/m fluoride (urban air)				0.04
1-2.5 mg/m fluoride (industrial exposure)				10-25
0.14-3.43 mg/m fluoride (industrial exposure)				1.4-34.3
12-26 mg/m fluoride (industrial exposure)				120-260
Cigarette smoking[b]				0.8

[a]Estimates for fluoride intake from drinking water assume consumption of 1 L/day drinking water for a 20 kg child, and 2 L/day for a 70 kg adult. Estimates for fluoride intake from air assume an inhalation volume for an adult of 20 m^3/day for non-occupational exposure or 10 m^3/working day for occupational (industrial) exposure.

[b]Fluoride dosage in mg/kg was not calculated for exposure to fluoride in air or in cigarette smoke because not all inhaled fluoride is absorbed. Figures given are estimates for the amounts of fluoride actually inhaled, but not necessarily absorbed.

Sources: United States Environmental Protection Agency, 1986; Federal Register, 1985b; World Health Organization, 1984; Hayes, 1982; Drury et al., 1980.

Table 1-2. Summary of Effects on Humans of Various Levels of Fluoride Intake

Description	Averaging Time	Intake or Exposure
4000-5000 ppm fluoride in bones	60 years	0.02-0.04 mg/kg/day 1 mg/L (water)
NOAEL (oral), RfD (oral) cariostatic effect, very mild dental fluorosis in about 1 in 5 people	0-12 years of age	0.06 mg/kg/day 1 mg/L (water)
LOAEL (oral) dental mottling, mild dental fluorosis	0-12 years of age	0.11 mg/kg/day 2 mg/L (water)
dental fluorosis common, sometimes severe	0-12 years of age	0.2-0.35 mg/kg/day >4 mg/L (water)
6000 ppm fluoride in bone, osteosclerosis, skeletal fluorosis	2-35 years, average of 8 years	0.2-1.0 mg/kg/day 8 mg/L (water) 0.14-3.43 mg/m3 (air)
crippling skeletal fluorosis	20 years; >2 years, dose dependant	0.2-10+ mg/kg/day >10 mg/L (water) 12-26 mg/m^3 (air)
no effect (oral)	acute	8-16 mg/kg
lethal (oral)	acute	32-64 mg/kg

[a] The information above is from human data. The estimates of fluoride intake and fluoride exposure levels are those reported in the cited publications; they were not derived by use of conversion factors. If an air concentration is not given in the table, assume that no information was found associating that effect with a particular airborne fluoride concentration.

Abbreviations: NOAEL - No Observed Adverse Effect Level
RfD - Reference Dose
LOAEL - Lowest Observed Adverse Effect Level

Sources: Heifetz and Horowitz, 1986; United States Environmental Protection Agency, 1986; Federal Register, 1985b; World Health Organization, 1984; Hayes, 1982; Drury et al., 1980.

Table 1-3. Summary of Official Standards and Human Toxicity Limits for Airborne Hydrogen Fluoride, Fluorine, and Fluorides

Standard or Effect	Hydrogen Fluoride mg/m³	Fluorine mg/m³	Fluorides as F mg/m³	Sources
Detection by smell	0.034[a]	0.28[b]	na	B
ACGIH - TWA (8-hr)	2.5	2	2.5	A
- STEL (15-min)	(ceiling)			
	na	4	na	A
NIOSH - TWA (8-hr)	2.5	na	2.5	F, G
- STEL (15-min)	5.0	na	na	F
OSHA - TWA (8-hr)	2.5[c]	0.2	2.5	C
No acute effect	2.6 (< 8 h)	15	na	E
Irritation (> 10 min)	13	na	na	E
(< 10 min)	26	25-40	na	E
IDLH	16.4[d]	50[e]	500	H
Breathing impossible	na	75	na	E
Lethal (LC_{LO}, 5 min)	41-205[f]	na	na	D
Lethal (LC_{100}, 60 min)	877[f]	na	na	E

na - data not available.

[a]Given as 0.042 ppm in the cited publication.
[b]Given as 0.14 ppm in the cited oublication.
[c]Given as 3 ppm in the cited publication.
[d]Given as 20 ppm in the cited publication.
[e]Given as 25 ppm in the cited publication.
[f]See Table 7-1 for other LC values.

Abbreviations: ACGIH - American Conference of Governmental Industrial Hygienists; IDLH - Immediately Dangerous to Life and Health; LC_{LO} - lowest lethal concentration for the exposed population (estimated); LC_{100} - lethal concentration for 100 percent of the exposed population (estimated); NIOSH - National Institute for Occupational Safety and Health; OSHA - Occupational Safety and Health Administration; STEL - Short Term Exposure Limit; TWA - Time Weighted Average.

Sources: A) American Conference of Governmental Industrial Hygienists, 1986.
B) Amoore and Hautala, 1983.
C) Code of Federal Regulations, 1985.
D) Halton et al., 1984.
E) Just and Emler, 1984.
F) National Institute for Occupational Safety and Health, 1976; 1975.
G) National Institute for Occupational Safety and Health, 1976.
H) Sittig, 1985.

2. Introduction

This report is intended to provide a brief review of the available information on the potential health effects associated with exposure to hydrogen fluoride and related compounds. Emphasis is placed on the potential health effects on the general public from exposure to ambient airborne concentrations. Sources, distribution, fate, and ambient levels of hydrogen fluoride and other inorganic fluorides are reviewed. Because most of the toxic effects of hydrogen fluoride are attributable to the fluoride ion, data concerning the pharmacokinetics, mutagenicity, carcinogenicity, teratogenicity, acute and chronic toxicity, and beneficial effects of both hydrogen fluoride and fluoride in general are discussed.

Fluorine (F) is the 13th most abundant element (Hodge and Smith, 1972). It is the most electronegative of all the elements, combining with almost all other elements (Stokinger, 1981); elemental fluorine is therefore not found in nature. Most naturally occurring fluorine is in the form of minerals, primarily fluorspar (fluorite, CaF_2), phosphate rock (fluorapatite, $CaF_2 \cdot 3Ca(PO_4)_2$), and natural cryolite (Na_3AlF_6; Levenson et al., 1982). Hydrogen fluoride is probably the most important of the numerous fluorine compounds, as it is used in the production of elemental fluorine (F_2) and in the synthesis of many other fluorine compounds, both organic and inorganic. Some HF is produced naturally by volcanic activity (Stokinger, 1981); most commercially used HF is produced by the reaction of sulfuric acid (H_2SO_4) with fluorspar to give HF and calcium sulfate (gypsum, $CaSO_4$; Levenson et al., 1982). Hydrogen fluoride is also produced as a by-product in industries using phosphate rock or cryolite.

Anhydrous hydrogen fluoride (HF) is a colorless, fuming, corrosive liquid or gas at room temperatures (boiling point, 19.54°C). Hydrogen fluoride is readily soluble in water and in a number of other solvents; aqueous HF is usually referred to as hydrofluoric acid. Anhydrous HF is one of the most acidic substances known, with a Hammet acidity function of -10.98 (Windholz et al., 1983); in aqueous solution, HF is a weak acid ($K_a = 6.46 \times 10^{-4}$ moles/liter). Hydrogen fluoride will attack glass, concrete, and certain metals, especially those containing silica (Weiss, 1980). Anhydrous HF actively dehydrates many organic materials, charring wood and paper on contact (Gall, 1980). Although not flammable itself, HF in contact with some metals may generate flammable hydrogen gas (Weiss, 1980). Polymerization of HF molecules due to hydrogen bonding occurs in the solid, liquid, and gaseous states (Gall, 1980). The strength of the hydrogen-fluorine bond, the hydrogen bonding and polymeric association of HF molecules, the strong acidity of anhydrous HF in contrast to its weak acidity in aqueous solution, and the absence of oxidation states of fluorine other than -1 are the most significant features of the chemistry of hydrogen fluoride (see Gall, 1980, for a review of hydrogen fluoride chemistry). Important chemical and physical properties of hydrogen fluoride and aqueous 70 percent hydrogen fluoride are summarized in Tables 2-1 and 2-2, respectively.

Hydrogen fluoride and hydrofluoric acid are used in a number of industries; since the 1930's, the two major uses of HF have been in aluminum

Table 2-1. Physical and Chemical Properties of Hydrogen Fluoride

Property		Source
Code Numbers:	CAS 7664-39-3 RTECS MW 7875000 (solution, MW 7890000) UN 1052 (anhydrous); UN 1790 (solution)	Sax (1984); Sittig (1985)
Chemical Name:	hydrogen fluoride	
Common Synonyms:	hydrofluoric acid; hydrofluoric acid gas; hydrofluoric acid, anhydrous; hydrofluoric acid solution; hydrofluoride; fluorhydric acid; antisal 2B; acide fluorhydrique (French); acido fluoridrico (Italian); fluorowodor (Polish); fluorwasserstoff (German); fluorwaterstof (Dutch); RCRA waste number U134; etching acid	MEDLARS II (HSDB, RTECS) (1986); Weast et al. (1986); Sax (1984); Anonymous 1981b)
Chemical Formula:	HF	
Common Aqueous Concentrations:	hydrofluoric acid: 40%, 42%, 48% reagent grade hydrofluoric acid: 48-51% grade hydrofluoric acid: 52-55% hydrofluoric acid	Chester et al.(1979) Weiss (1980) technical Weiss (1980) 70% grade Weiss (1980)
Formula Weight:	20.006	Gall (1980)
Composition, wt %:	H, 5.038 F, 94.96	Gall (1980) Gall (1980)
Molecular Weight:	saturated vapor at boiling point 78.24 saturated vapor at 100°C 49.08	Gall (1980) Gall (1980)
Polymerization:	exists as an associated molecule up to H_6F_6 at 1 atm and temperatures below 100°C; average molecular weight 50-55.	Stokinger (1981)

(continued)

Table 2-1. Continued

Property		Source
Physical State:	colorless fuming corrosive liquid or gas	Weast et al. (1986)
Melting Point:	-83.1°C	Weast et al. (1986)
Boiling Point:	19.54°C	Weast et al. (1986)
Refractive Index:	gas, nD_{20}, 1.90	Weast et al. (1986)
Density:	0.921 g/L at 0°C (gas)	Stokinger (1981)
	1.002 g/cm^3 at 0°C (liquid)	Gall (1980)
	0.9576 g/cm^3 at 25°C (liquid)	Gall (1980)
	3.553 mg/cm^3 at 25°C (saturated vapor)	Gall (1980)
	3.979 mg/cm^3 at 34C° (saturated vapor)	Gall (1980)
Solubility:		
cold water	infinite	Weast et al. (1986)
hot water	very soluble	Weast et al. (1986)
alcohol	very soluble	Windholz et al. (1983)
ether	slightly soluble	Windholz et al. (1983)
benzene	2.54 (wt % at 5°C)	Windholz et al. (1983)
toluene	1.80 (wt % at 5°C)	Windholz et al. (1983)
m-xylene	1.28 (wt % at 5°C)	Windholz et al. (1983)
tetralin	0.27 (wt % at 5°C)	Windholz et al. (1983)
Many compounds are soluble in HF.		Windholz et al. (1983)

(continued)

Table 2-1. Continued

Property		Source
Acidity:		
Anhydrous HF is one of the most acidic substances known		Windholz et al. (1983)
Hammett acidity function (H_0) = -10.98		Windholz et al. (1983)
HF is a weak acid in aqueous solution		Windholz et al. (1983)
Ka = 6.46 x 10^{-4} moles/liter		Windholz et al. (1983)
K (25°C, 0.1-0.01 N) = 3.53 x 10^{-4}		Weast et al. (1986)
pK (25°C, 0.1-0.01 N) = 3.45		Weast et al. (1986)
Vapor Pressure:	10 mm Hg at -65.8°C	Weast et al. (1986)
	40 mm Hg at -45.0°C	Weast et al. (1986)
	100 mm Hg at -28.2°C	Weast et al. (1986)
	360 mm Hg (48.025 kPa) at 0.028°C	Boublík et al. (1984)
	394 mm Hg (52.503 kPa) at 2.449°C	Boublík et al. (1984)
	532 mm Hg (70.971 kPa) at 10.006°C	Boublík et al. (1984)
	760 mm Hg (101.325 kPa) at 19.738°C(nbp)	Boublík et al. (1984)
	912 mm Hg (121.650 kPa) at 25.000°C	Boublík et al. (1984)
	1084 mm Hg (144.560 kPa) at 29.954°C	Boublík et al. (1984)
In general, for HF, log Po = 6.93862 - 1571.203 / (t + 298.777), where P° is the vapor pressure in kPa and t is the temperature in °C; 101.325 kPa = 1 atm = 760 mm Hg		Boublík et al. (1984)

(continued)

Table 2-1. Continued

Property		Source
Heat of Solution:	-14,700 cal/mole (gas) -734.6 cal/g	Weast et al. (1986) Weiss (1980)
Latent Heat of Vaporization:	80.5 cal/g	Weiss (1980)
Critical Temperature:	188°C	Gall (1980)
Critical Pressure:	64.2 atm (6.480 MPa)	Gall (1980)
Critical Density:	0.29 g/cm^3	Gall (1980)
Partition Coefficients:		Hansch and Leo (1979)
diethyl ether/water:	log P = -0.64	
$CHCl_3$/water	log P = -2.92	
Odor:	sharp, pungent, irritating	Weiss (1980)
Odor Threshold:	0.042 ppm (v/v) 0.03 mg/m^3 (0.04 ppm)	Amoore and Hautala(1983) Weiss (1980)
Biological Oxygen Demand:	None	Weiss (1980)
Conversion Factors (vapor):	1 ppm = 0.82 mg/m^3 = 0.00082 mg/L 1 mg/m^3 = 1.22 ppm 1 mg/L = 1223 ppm	Chester et al. (1979)
Reactivity:	Dissolves in water with liberation of heat; will attack glass, concrete, and certain metals, especially those containing silica; will attack natural rubber, leather, and many organic materials; may generate flammable hydrogen gas in contact with some metals.	Weiss (1980)

Table 2-2. Physical Properties of Aqueous Seventy Percent Hydrogen Fluoride

Boiling Point:	66.4°C
Freezing Point:	-69°C (solid phase is $HF \cdot H_2O$
Vapor Pressure:	150 mm Hg (20 kPa, 2.9 psia) at 25°C
Density:	1.22 g/cm^3 at 25°C

Source: Gall (1980)

manufacture and fluorocarbon production (Levenson et al., 1982; Gall, 1980; Stuewe, 1958). Other important uses for HF include uranium processing, petroleum alkylation, stainless steel pickling, etching of glass and semiconductor components, and the production of synthetic cryolite, fluorine gas, fluoride salts, fluorine-containing plastics, and special metals. End uses of other fluoride compounds include water fluoridation (for prevention of dental caries), ore flotation, wood preservation, electroplating, and chemical cleaning. The consumption of hydrogen fluoride by the major U.S. industries is given in Table 2-3 for the years 1957 (near the beginning of rapid growth in HF usage), 1974 (at the peak of HF usage in the aluminum and fluorocarbon industries), and 1981 (more typical of recent HF consumption following the effects of the economic recession on aluminum production and of environmental legislation on fluorocarbon production). Total HF consumption in the U.S. was between 320 and 340 thousand metric tons from 1975 to 1981 (Levenson et al., 1982); HF consumption was 277 thousand metric tons in 1985 and is expected to reach 318 thousand metric tons) by 1989 (Chemical Marketing Reporter, 1986). U. S. fluorspar and hydrogen fluoride production have been generally decreasing since 1974 (Table 2-4). The decrease in HF production has been larger than the decrease in HF consumption; imports of HF to the U. S. have been showing a corresponding increase. Mexico and Canada are the principal sources of imported HF. Most of the fluorspar used in the U. S. is also imported, primarily from Mexico and the Republic of South Africa (Levenson et al., 1982). About fifty to seventy percent of U. S. fluorspar consumption is for HF production; most of the rest of the fluorspar goes directly to steel production (Table 2-4), where it is used to increase the fluidity of the slag. The steel industry, and therefore the consumption of fluorspar by the steel industry, is highly dependent on economic factors. Steel-making processes have also been changing, from mostly open hearth production to mostly basic oxygen or electric processes, and this also affects fluorspar consumption by the industry (Levenson et al., 1982).

Total industrial emission of soluble fluoride in the United States (around 1964-1970) was an estimated 140 to 150 thousand metric tons per year (Smith and Hodge, 1979; Krook and Maylin, 1979a), and in Canada (1972) about 14 thousand metric tons per year (Krook and Maylin, 1979a). The emission rate for hydrogen fluoride in the U.S. in 1980 from HF manufacture, aluminum production, phosphate processing, and coal combustion was an estimated 81.5 thousand metric tons per year (Misenheimer et al., 1985). Volcanic and fumarolic activity (throughout the world) is estimated to contribute up to 7.3 million metric tons of fluoride per year to the atmosphere (Bartels, 1972; Carpenter, 1969).

Several comprehensive reviews exist on occupational exposure to and risks from fluorides or HF, the effects of HF or fluorides on plants and animals, and health and environmental effects of fluorides (see for instance Smith, 1986b; World Health Organization, 1984; Jahr, 1983; Smith et al., 1982; van

Haut and Krause, 1982; Drury et al., 1980; Safe Drinking Water Committee, 1980; 1977; Smith and Hodge, 1979; Hodge and Smith, 1977; National Institute for Occupational Safety and Health, 1976; 1975; National Research Council, 1974; 1971; Hodge and Smith, 1965). This report seeks to concentrate on the effects of human health that can be expected from ambient airborne concentrations of hydrogen fluoride and other fluorides.

Table 2-3. U. S. Hydrogen Fluoride Consumption[a]

Use	1957 HF	1957 % of Total	1974 HF	1974 % of Total	1981 HF	1981 % of Total
Fluorocarbons	35.0	28.5	164.0	44.0	137.0	42.0
Aluminum production[b]	48.0	39.0	139.0	37.0	103.0	31.0
Gasoline alkylation catalyst	5.5	4.5	13.0	3.5	16.0	5.0
Stainless steel pickling	6.4	5.0	13.0	3.5	10.0	3.0
Uranium production	14.5	12.0			(6-9)[c]	
Conversion to salts	6.8	5.5			(>4)	
Etching: glass	1.8	1.5			(2-4)	
semiconductors					(>5)	
Other uses	4.6	4.0	46.0	12.0	62.0	19.0
Total	122.6	100.0	375.0	100.0	328.0	100.0

Sources: Stuewe (1958); Levenson et al. (1982).

[a]Thousands of metric tons, 100% HF.

[b]Includes both aluminum fluoride and synthetic cryolite.

[c]Numbers in parentheses indicate approximations that were not used in calculating totals.

Table 2-4. U.S. Fluorine Sources and Consumption

	1957	1970	1974	1980	1981	1982	1983	1984	1985
Fluorspar Production[a]	293	229	189	81	101	69	--	--	--
Fluorspar Imports[a]	572	991	1212	816	750	493	411	639[g]	--
Fluorspar Consumption[a]									
steel[b]	219	502	584	331	344	179	160	168[g]	--
hydrofluoric acid	298	681	748	533	477	283	327	424[g]	--
other[c]	68	62	51	22	25	19	25	25[g]	--
total[d]	585	1245	1383	886	846	481	512	617[g]	--
HF Production[a]									
withdrawn from system	--	218	255	193	162	123	174	152	--
not withdrawn from system		77	90	49[g]	--	--	--	--	--
total[d]	135	295	346	242[g]	217[h]	219[h]	149[h]	193[h]	--
HF Imports[a]	--	1	30	90	96	93	83	104	--
HF Consumption[e]	123	296	375	322	328	--	--	--	277
Other Fluorine Sources[f]									
production and imports[a]	43	79	126	115	90	70	89	--	--

Sources: Steuwe (1958); Levenson et al. (1982); SRI International (1985); Chemical Marketing Reporter (1986).

- data not available.

[a]Thousands of metric tons.

[b]Includes open hearth, basic oxygen, and electric furnace processes.

[c]Includes iron and steel castings and glass.

[d]Totals may not equal the sums of categories because of conversion to metric units and rounding.

[e]Thousands of metric tons, 100% HF.

[f]Includes hydrofluosilicic acid, sodium silicofluoride, and cryolite; consumption is approximately equal to production and imports.

[g]Amounts estimated (Levenson et al., 1982).

[h]Amounts estimated from fluorspar consumption data, 2.2 metric tons of fluorspar per metric ton of HF produced (Levenson et al., 1982; SRI International, 1985).

3. Air Quality and Environmental Fate

3.1. Sources

The only known natural source of hydrogen fluoride is volcanic activity (Stokinger, 1981). Masaya Volcano in Nicaragua, for instance, emits 5 metric tons of HF per day during its active degassing phase (Baxter et al., 1982). The kinds and amounts of gases emitted vary between volcanoes, and in most cases HF is not the major component of the emissions. A number of other inorganic fluoride compounds are also present in volcanic emissions, including F_2, NH_4F, KF, NaF, CaF_2, MgF_2, SiF_4, $(NH_4)_2SiF_6$, Na_2SiF_6, K_2SiF_6, and KBF_4 (Smith and Hodge, 1979); trace amounts of a few fluorine-containing organic compounds have also been identified in the emissions. Fluorine or fluoride compounds have been found in the emissions of volcanoes in Alaska, Hawaii, Central America, Iceland, New Zealand, the Azores, the Canary Islands, Martinique, and several places in Europe and Asia. Total fluoride concentrations in fumarole condensates of several Central American volcanoes range from <0.1 to 200 mg/kg (Smith and Hodge, 1979); the total worldwide contribution of fluoride to the atmosphere by volcanic and fumarolic activity has been estimated to be 1 million metric tons of fluoride per year (Carpenter, 1969; Bartels, 1972, estimates it to be 7.3 million metric tons per year).

Natural sources of other airborne fluoride compounds include ocean spray and dust from the weathering of fluoride-containing rocks or soils (Smith and Hodge, 1979). Fluoride concentrations in rocks range from 80 to 4700 mg/kg and in soils from traces to 7070 mg/kg with means around 200 to 300 mg/kg. Fresh water sources in North America contain 0 to 16 mg/L fluoride, depending on the minerals the water comes in contact with and several other factors such as temperature and pH (Smith and Hodge, 1979). Airborne dust collected at sea is thought to derive from continental or volcanic rocks, since its fluoride content, which ranges from 330 to 875 mg/kg, approximates that of crustal rocks. Seawater itself typically contains 1.2 to 1.4 mg/L dissolved fluoride, about half of which is thought to be present as MgF^+ (Carpenter, 1969). Essentially all of the fluoride-containing dust is thought to remain in a particulate form, eventually settling out on land or over water, where it sediments (Carpenter, 1969). Sea salt may contribute a variable amount of dissolved fluoride to the air (see Carpenter, 1969; Mahadevan et al., 1986), but it does not appear to be a major source of airborne fluoride (Barnard and Nordstrom, 1982).

Anthropogenic sources of hydrogen fluoride and other fluorides include coal-burning facilities and industries which produce or consume hydrogen fluoride or other fluorides, especially the steel, aluminum, and phosphate rock (fertilizer) industries (Table 3-1). Total soluble fluoride emissions from industrial sources were 140 to 150 thousand metric tons per year in the U. S. around 1970 (Krook and Maylin, 1979a; Smith and Hodge, 1979); the U. S. emission rate for hydrogen fluoride from HF manufacture, aluminum production, phosphate processing, and coal combustion was an estimated 81.5 thousand metric tons per year in 1980 (Misenheimer et al., 1985; this

Table 3-1. Fluoride Emissions to the Atmosphere by Industrial Sources in the United States[a]

Source	Total Fluoride (1968-1970)	HF (1980)
Coal combustion for power	24.1	63.2
Steel	58.6	b
Phosphate rock processing	19.3	6.2
Aluminum processing	14.7	12.1
HF production	0.6	0.02
Miscellaneous sources	32.9	b
Total	150.2	81.5

Sources: Boscak (1978); Krook and Maylin (1979a); Smith and Hodge (1979); Misenheimer et al. (1985).

[a]Data given in thousands of metric tons per year.

[b]Data not available.

report assumes that all the fluorine emitted from coal combustion is in the form of HF but admits that this has not yet been demonstrated). Hydrogen fluoride production is a minor source of flucride emission when compared with the aluminum, phosphate, or steel industries, or with coal combustion (Table 3-1). Steel production is one of the major sources of fluoride emissions (mostly particulate fluorides from the fluorspar in the flux), although fluorides are not the major emission from steel plants (United States Environmental Protection Agency, 1977). Coal combustion is probably the other major source of fluoride emission (various coals contain up to 141 mg/kg fluorine with a mean of 74 mg/kg; Misenheimer et al., 1985), although again, HF (or other fluoride compounds) is not the major emission from coal burning facilities. Total worldwide fluoride (soluble and particulate) emissions from industrial sources were estimated to have been 3.6 million metric tons in 1972 (Barnard and Nordstrom, 1982).

Emission factors for HF, particulate fluorides, or SiF_4 are available for coal combustion, HF manufacture, frit manufacturing, phosphate processing, and the various methods and steps of aluminum and steel production (Misenheimer et al., 1985; United States Environmental Protection Agency, 1984; 1983; 1980a; 1980b; 1977). These give an emission rate for a pollutant in terms of amount of a substance consumed or produced. For instance, the emission factor for HF production in the absence of any emission controls is 12.5 kg HF emitted per metric ton of HF produced (25.0 lbs/ton; Misenheimer et al., 1985); when emission control (a caustic scrubber) is used, the emission factor is 0.1 kg/metric ton of acid produced (0.2 lbs/ton). By using a production figure for HF of 193 thousand metric tons per year (the amount of HF produced and withdrawn from the system in the United States in 1980; Levenson et al., 1982; see Table 2-4, p. 2-9) together with the emission factors given above, estimates of 2.4 and 0.02 thousand metric tons HF per year are obtained for uncontrolled and controlled emissions, respectively, from HF production in the United States. Actual HF emissions from HF production in 1980 are in fact estimated to be 0.02 thousand metric tons (21.3 tons; Misenheimer et al., 1985; see Table 3-1). Actual amounts of U. S. fluoride (including HF) emissions have been changing in recent years due to changes

in industrial methodology (from primarily open hearth to basic oxygen processes in steel production, for instance), increasing efficiency of emission controls, and various economic considerations. The steel and aluminum industries in particular are highly dependent on economic conditions in terms of total production; it is also becoming economically desirable to recycle as much fluorine or fluoride as possible in the aluminum and petroleum alkylation industries (Levenson et al., 1982).

Gaseous fluorides commonly make up 20 to 40 percent of industrial fluoride emissions (Barnard and Nordstrom, 1982; both Alary et al., 1981, and Krook and Maylin, 1979a, give around 50 percent for specific factories). Most of these gaseous fluorides are in the form of HF or SiF_4, but H_2SiF_6, BF_3, and F_2 may also be emitted from the glass and phosphate industries (Smith and Hodge, 1979) and UF_6 from uranium processing facilities (Bostick et al., 1985). Common particulate fluorides released from industrial sources include Na_3AlF_6, AlF_3, $Na_5Al_3F_{14}$, CaF_2, NaF, Na_2SiF_6, PbF_2, and $Ca_{10}(PO_4)_6F_2$ (Smith and Hodge, 1979).

Hydrogen fluoride is found in the stratosphere (about 12 km altitude) at a latitude-dependent column amount of about 1.4 to 5.4 x 10^{14} molecules per square cm (Mankin and Coffey, 1983). This HF is almost entirely from decomposition of chlorofluoromethanes of anthropogenic origin, and seems to be increasing at a rate of about 12 percent per year. Unlike chlorine, fluorine does not react with ozone, so that HF in the stratosphere is stable. The HF gradually diffuses to the troposphere, where it is rained out (Mankin and Coffey, 1983).

3.2 Distribution and Fate

The major gaseous fluorides released to the environment, HF and SiF_4, are both readily hydrolyzed and dispersed in the atmosphere (Barnard and Nordstrom, 1982). Anhydrous HF combines with water vapor in the air to form aqueous hydrofluoric acid (National Research Council, 1971). Several volatile inorganic fluorides, including SF_4, S_2F_2, and fluorine gas and other halogen fluorides, as well as SiF_4, give rise to hydrolysis products which are less volatile and which are eventually removed from the atmosphere by condensation or nucleation processes (Drury et al., 1980; see National Research Council, 1971, for a discussion of fluoride chemistry in the atmosphere). Uranium hexafluoride, UF_6, also hydrolyzes to form a less volatile product, UO_2F_2, plus HF (Bostick et al., 1985). Uranium compounds pose a greater health hazard in terms of their radioactivity than their fluoride content; for that reason stringent controls are practiced and emissions of UF_6 and related compounds are normally very small (Drury et al., 1980; see also Bostick et al., 1985), although accidental releases do occur (see for instance Murphy, 1986).

Most particulate fluorides of industrial origin are stable compounds and do not hydrolyze (Drury et al., 1980); most of these settle to the ground as dusts. The availability of the fluoride in these compounds to plants or to herbivores is dependent on the solubility of the compounds, which varies between compounds and also between solvents. NaF is readily soluble in water, while CaF_2 is essentially insoluble. Fluorapatite is insoluble in water, but it is at least somewhat soluble in the gastrointestinal tracts of animals which ingest it as dust on their forage (National Research Council, 1971).

Atmospheric precipitation is probably the main route for removal of airborne fluoride compounds (Mahadevan et al., 1986; Barnard and Nordstrom, 1982). Total inorganic fluoride concentrations (including all F from hydrogen fluoride or other fluoride compounds) up to 14.1 mg/L, depending on proximity

to industrial activities, have been measured in rain- and snowfall (Smith and Hodge, 1979). Mahadevan et al. (1986) found an average fluoride concentration in precipitation of 3 to 5 µg/L (range, 1 to 12 µg/L) for background (nonindustrialized) sites in India and 20 µg/L or more for industrial areas. The calculated contribution of soil fluoride to precipitation was 0.6 µg/L. A variable amount of fluoride contribution from sea salt was demonstrated for coastal and marine areas; the total fluoride in the precipitation in these areas was still much less than for the industrial areas.

Barnard and Nordstrom (1982) obtained a mean background fluoride concentration in precipitation of 8.1 µg/L (range, 0 to 18 µg/L) for nonindustrial sites in the eastern United States. They were unable to demonstrate a fluoride contribution from sea salt. From their estimate of 3.6 million metric tons of fluoride released to the atmosphere from industrial sources (worldwide) in 1972, they calculate a fluoride concentration in rainfall of 7.6 µg/L. If maximum fluoride contributions from dust (1 µg/L) and volcanic activity (2 to 3 µg/L) are added to that figure, a maximum rainfall fluoride concentration of 11.6 µg/L is obtained. Because there is no volcanic activity in the eastern United States (and therefore the maximum expected concentration of fluoride in the rainfall is 8.6 µg/L), Barnard and Nordstrom conclude that most fluoride in atmospheric precipitation is of anthropogenic origin. Fluoride in precipitation eventually ends up in the soil and the ground water.

3.3. Ambient Levels

Ambient air concentrations of total inorganic fluoride (including fluoride from HF and any other fluoride compounds) or of gaseous and particulate fluorides have been measured at various industrial and nonindustrial sites. Similar measurements for hydrogen fluoride alone are generally not available. In rural air, away from any industrial sources of fluoride, only traces ($< < 1$ µg/m^3) of fluoride are found (Hodge and Smith, 1972). The amount of airborne fluoride is higher in urban areas, due both to industrial pollution and to the burning of coal and other fluoride-containing fuels; the increased burning of fuels in the winter months can cause additional increases in the fluoride content of urban air (World Health Organization, 1984). Even so, the atmospheric fluoride concentrations in urban areas rarely reach 2 µg/m^3 (World Health Organization, 1984). In several studies of urban communities in the U.S. and Europe, fluoride concentrations up to 3.8 µg/m^3 were measured; most samples contained less than 2.0 µg F/m^3 (World Health Organization, 1984; Drury et al., 1980).

Air in the immediate vicinity of industrial operations can contain larger amounts of fluoride (World Health Organization, 1984; Drury et al., 1980). Local airborne fluoride concentrations of 140 to 220 µg/m^3 have been measured near European aluminum plants (Drury et al., 1980). Near some other industrial locations (primarily aluminum or phosphate processing plants), in communities in which fluoride effects have been reported or studied, airborne fluoride concentrations (when reported) ranged from 2.5 to 14,000 µg F/m^3 (Smith and Hodge, 1979), although in most of these cases concentrations were less than 100 µg/m^3. Smith and Hodge (1979) list more recent ambient air fluoride concentrations near industrial operations of several types and state that mean concentrations were nearly always less than 8.2 µg/m^3 (10 ppb).

Ambient air fluoride concentrations measured 1.5 km downwind from an aluminum processing plant in New York averaged 0.36 µg/m^3 gaseous fluoride and 0.71 µg/m^3 total fluoride over a six month period (Krook and Maylin,

1979a). The maximum fluoride concentrations measured for a twelve-hour period were 6.41 μg/m^3 gaseous and 11.94 μg/m^3 total fluoride. At a location 4 km from the plant, the six-month averages were 0.28 μg/m^3 gaseous and 0.43 μg/m^3 total fluoride; the twelve-hour maximums were 2.05 μg/m^3 gaseous and 5.26 μg/m^3 total fluoride. Air fluoride concentrations in the vicinity of the Paducah (Kentucky) Gaseous Diffusion Plant reached a maximum of 1.5 μg/m^3 HF (1.8 ppb, from weekly measurements) in 1984 (Martin Marietta Energy Systems, Inc., 1985); average fluoride concentrations at most sampling sites were less than 0.082 μg/m^3. In general, fluoride concentrations near industrial sources are probably decreasing due to improved emission control standards and technology (World Health Organization, 1984).

3.4. Exposure

In the middle 1970s in the United States, an estimated 22,000 workers in 57 occupations were potentially exposed to hydrogen fluoride (National Institute for Occupational Safety and Health, 1976), and 350,000 workers in 92 occupations were potentially exposed to various inorganic fluorides (National Institute for Occupational Safety and Health, 1975). Although recent figures are not available, the number of workers exposed to fluorides or hydrogen fluoride is probably somewhat smaller now because of the general decrease in the major industries which produce or use HF or other fluoride compounds.

The Occupational Safety and Health Administration (OSHA) gives a federal occupational exposure standard for hydrogen fluoride of 2.5 mg/m^3 (stated as 3 ppm) for an 8-hour time-weighted-average (TWA); the 8-hour TWA is 2.5 mg F/m^3 air for fluoride in general, including fluoride in dust, and 0.2 mg/m^3 (0.1 ppm) for elemental fluorine (Code of Federal Regulations, 1985). The American Conference of Governmental Industrial Hygienists (1986) recommends threshold limit values (TLVs) of 2.5 mg/m^3 (3 ppm; this is a ceiling value, not to be exceeded at any time) for hydrogen fluoride, 2.5 mg/m^3 (TWA) for fluorides as F, and 2 mg/m^3 (1 ppm) for fluorine. A short term exposure limit (STEL, a 15-minute TWA) of 4 mg/m^3 (2 ppm) is also given for fluorine. The National Institute for Occupational Safety and Health (1976; 1975) lists similar exposure limits for both hydrogen fluoride and fluorides, with the addition of a ceiling on short term exposure to HF of 5.0 mg F/m^3 (6 ppm) for 15 minutes. Current occupational exposure limits in other countries are comparable to or lower than the limits in the United States (International Labour Office, 1984). Occupational exposure to fluoride has been much higher in the past than now, and much of the available information concerning the effects of fluoride on humans has come from studies of occupational fluoride exposure. Under current exposure limits, a maximum of 10 to 25 mg of fluoride could be inhaled in a working day (World Health Organization, 1984). Occupational exposure to fluoride or hydrogen fluoride is treated at length by the National Institute for Occupational Safety and Health (1976; 1975) and by Hodge and Smith (1977; see also Smith and Hodge, 1979).

Exposure of the general public to hydrogen fluoride or other airborne fluorides is greatest in the vicinity of point sources such as active volcanoes, HF manufacturing plants, plants which use HF or fluorspar (including aluminum, steel, and petroleum alkylation plants), and coal-burning facilities. An estimated 1,075,000 people live within 8 km of 11 HF-manufacturing plants in the United States (Boscak, 1978); the figure naturally is higher when the other fluoride or HF sources are considered. Average total fluoride concentrations in the vicinity of industrial operations in the U. S. and Canada

are normally less than 8.2 μg/m^3 (10 ppb) (Smith and Hodge, 1979; see also Krook and Maylin, 1979a). Several states have ambient air standards for fluorides (Chester et al., 1979); these range from 0.8 μg/m^3 (Montana) to 5 μg/m^3 (Pennsylvania) over a 24-hour period for fluoride as HF. The American Industrial Hygiene Association in 1969 recommended a Community Air Quality Guide for HF of 2.8 μg/m^3 (3.5 ppb) for 24 hours (Chester et al., 1979). These standards were established to protect vegetation and livestock; cattle health may not in fact be adequately protected by these standards (Krook and Maylin, 1979a), but these fluoride levels are well below those thought to cause adverse health effects in humans (Chester et al., 1979).

People living in rural locations away from sites of industrial operations are exposed to only trace amounts of airborne fluoride; people living in cities or in industrial areas are exposed to proportionately more airborne fluoride. It has been estimated that an individual living in London might inhale 0.001 to 0.004 mg of fluoride per day, possibly 5 to 10 times higher on an extremely foggy day with high pollution (Martin and Jones, 1971, as cited in Smith and Hodge, 1979); in heavily industrialized areas, a person might inhale at most 0.01 to 0.04 mg of fluoride per day (0.0025 and 0.06 mg/day in two other studies; see Smith and Hodge, 1979; World Health Organization, 1984). Near one aluminum plant an estimated 0.4 to 0.7 mg fluoride per day was inhaled per person (Smith and Hodge, 1979), but this was probably an extreme situation. If one assumes a high value of 2 μg F/m^3 air (see section 3.3 above) in urban areas, and an inhalation volume for an adult of 20 m^3 air per day, the amount of fluoride inhaled would be 0.04 mg/day (World Health Organization, 1984). If the airborne fluoride concentration near an industrial site were 8 μg/m^3 (about 10 ppb), an adult could expect to inhale as much as 0.16 mg fluoride per day. Acute exposure to gaseous HF rarely occurs in a nonoccupational setting, but HF is one of several potentially toxic gases which may be encountered in fires (Hilado and Cumming, 1978; Hilado and Furst, 1976).

The general population probably receives more fluoride via food and drinking water than from the air. Most food items contain traces of fluoride, and some items, particularly tea and seafood, can contain substantially more. Fluoride intake from food ranges from 0.25 to 1.5 mg per day (Smith and Hodge, 1979; see also Anonymous, 1986); leafy vegetables grown near industrial fluoride sources may increase dietary fluoride by 1 to 1.7 percent. Water sources in the United States may contain from 0.1 to 4 or more mg/L fluoride (Safe Drinking Water Committee, 1980; Smith and Hodge, 1979). In 1980, 120 million Americans lived in areas with artificially fluoridated water supplies (Anonymous, 1986); this water typically contains 1 mg/L fluoride in temperate regions. Estimates for total fluoride intake from food, water, and other beverages for people in fluoridated areas range from 1 to 5.4 mg per day (World Health Organization, 1984; Safe Drinking Water Committee, 1980; Smith and Hodge, 1979); 2 to 3 mg per day is probably typical, although individual and population variations in fluoride intake probably exist.

Some individuals will also be exposed to as much as 0.8 mg of fluoride per day from heavy cigarette smoking (Drury et al., 1980). Other potential sources of fluoride to humans include fluoridated dentifrices and mouthwashes (average about 0.25 mg/day); accidental intake, especially by children, of dentifrices (see Heifetz and Horowitz, 1986) or of sodium fluoride pesticides; exposure to fluoride-containing anaesthetic gases; and medically prescribed use of fluoride in the treatment of osteoporosis (World Health Organization, 1984). For most people (those who do not have occupational exposure to fluorides or hydrogen fluoride), the major source of fluoride is their food and water. The average daily fluoride intake for people who are not in the

immediate vicinity of industrial operations is on the order of 2 to 3 mg per day from food and water and less than 0.1 mg fluoride per day from inhaled fluoride.

4. Pharmacokinetics

4.1. Absorption

Inhaled fluorides consist primarily of HF and particulate fluorides, both of which can be deposited in the respiratory tract (World Health Organization, 1984). Hydrogen fluoride, most of which is probably deposited in the upper respiratory tract, is rapidly absorbed into the system, either directly from the respiratory tract or following translocation to the gastrointestinal tract via nasal mucus (Morris and Smith, 1982). Close to 100 percent of inhaled HF is absorbed (Machle and Largent, 1943). Depending on the size and nature of the particles, fluoride-containing particles may be exhaled without being deposited on the surface of the respiratory tract, or they may be deposited in the nasopharynx, the tracheobronchial tree, or the alveoli (World Health Organization, 1984). Absorption of these fluorides and of ingested fluorides is dependent on several factors, including the chemical nature of the fluorides and what other substances have also been ingested. Fluoride from inhaled dust is absorbed as rapidly as fluoride from inhaled HF, but for a given airborne fluoride concentration, less total fluoride is absorbed from fluoride-containing dust than from gaseous fluoride compounds (Collings et al., 1951). Soluble fluoride salts (e.g., fluorides in fluoridated water) are absorbed very rapidly by the gastrointestinal tract. The presence of fluoride-binding cations such as calcium or aluminum will result in greatly reduced fluoride absorption in the gastrointestinal tract (World Health Organization, 1984; Drury et al., 1980; Spencer et al., 1980), thereby increasing fluoride excretion in the feces. In experiments with human subjects, Machle and Largent (1943) observed approximate gastrointestinal absorptions of 97 percent for NaF and 95 percent for CaF_2 administered in solution. Only 60 percent of solid CaF_2 was absorbed in the gastrointestinal tract, the rest being excreted in the feces. The low pH of the stomach permits some otherwise insoluble fluoride compounds to be dissolved, causing generation of HF gas in the stomach (World Health Organization, 1984). Hydrogen fluoride is rapidly absorbed from the gastrointestinal tract, as from the respiratory tract; absorption of HF through the skin has also been observed in workers suffering hydrofluoric acid burns in accidents (World Health Organization, 1984; Tepperman, 1980; Burke et al., 1973).

Absorption of any fluoride appears to be a passive process (Drury et al., 1980). Fluoride from any source is thought to be transported across biological membranes primarily as molecular HF (Whitford and Pashley, 1984; Gutknecht and Walter, 1981; Whitford et al., 1976). At physiological pH (in blood, intracellular fluid, or mucus), fluoride from any source exists primarily as fluoride ion (F^-), although a small amount of molecular HF exists in equilibrium with the ion. The fate or effects of absorbed inorganic fluoride are essentially independent of the fluoride source.

4.2. Retention and Distribution

Approximately 35 to 50 percent of absorbed fluoride from any source is retained in the human body (World Health Organization, 1984; Hodge and Smith, 1965); the (human) subjects of Machle and Largent (1943) demonstrated about 60 percent retention of absorbed fluoride (total daily intake, >6.0 mg/day). At low fluoride intakes (non-occupational, <4.0 to 5.0 mg/day), there may be very little cumulative storage of fluoride (McClure et al., 1945). About 99 percent of retained fluoride is found in the skeleton, the rest in the blood and in other tissues (World Health Organization, 1984). Fluoride is transported through the body via the bloodstream. About three-fourths of the blood fluoride is in the plasma; the remainder is in or on the red blood cells (World Health Organization, 1984). At least one-half of the fluoride in human serum may be nonionic fluoride; this includes both organic fluoride (perfluorinated fatty acid derivatives) and nonionizable fluoride formed from F^- or HF, and the amount of nonionic fluoride is related to the total fluoride intake (World Health Organization, 1984; Morris and Smith, 1983; Ophaug and Singer, 1977).

For the general population at a steady-state exposure to fluoride, the plasma concentration of inorganic (ionic) fluoride is directly related to the inorganic fluoride content of the drinking water (World Health Organization, 1984; Drury et al., 1980). The normal range of plasma fluoride concentrations is about 10 to 20µg/L in areas with low water fluoride levels (less than or equal to 1 mg/L; World Health Organization, 1984; Drury et al., 1980; Smith and Hodge, 1979). An average blood fluoride concentration of about 82 µg/L was found in a community with 5.6 mg/L fluoride in the drinking water (Drury et al., 1980; Smith and Hodge, 1979). Blood fluoride levels in fatal cases of acute fluoride poisoning have ranged from 3.5 to 15.5 mg/L (Gosselin et al., 1984). Plasma concentrations of fluoride increase with age, possibly because clearance from the blood via uptake into bone is slower in adults than in children. Clearance of fluoride from the blood occurs rapidly by incorporation into bone and by renal absorption and excretion. Young bone (i.e., in children), presumably because it is less saturated with fluoride, appears to take up fluoride more rapidly than does bone in older individuals; children therefore excrete less fluoride in the urine than do adults.

The fluoride ion taken up by bone replaces hydroxyl ions in bone apatite (World Health Organization, 1984). The precise mechanism of fluoride incorporation into bone is still under investigation (see World Health Organization, 1984; Rioufol et al., 1983; Drury et al., 1980); the overall result is that absorbed fluoride is incorporated into the hard tissues primarily by an exchange process (the displacement of hydroxyl groups) and by incorporation into the apatite lattice during bone mineralization. The amount of fluoride in bone is dependent on an individual's age, sex, fluoride intake, and the specific type and part of bone being examined. Fluoride accumulates in the bone with increasing age, although the rate of incorporation decreases; higher bone fluoride concentrations are also found in individuals or groups with greater fluoride exposure. Long-term (60 years) intake of 1 mg/L fluoride in water can cause a fluoride level of 4000 mg/kg of dry fat-free bone (Drury et al., 1980). An intake of 8 mg/L for 35 years would cause a bone fluoride level of 6000 mg/kg, the level necessary for detection of osteosclerosis, which is defined as an increased opacity of the bone to X-rays. Surface regions of bones incorporate fluoride more rapidly than interior regions, and cancellous (spongy) bone more than cortical (compact) bone. Fluoride can be released from bone (when intake decreases), and has a removal half-life of 8 to 10

years (Grandjean, 1982; Drury et al., 1980; Forbes et al., 1978). If fluoride intake is decreased following a period of fluoride storage, the urinary fluoride level may exceed the current fluoride intake, resulting in a net loss of fluoride from the body (Grandjean, 1982; Largent, 1952). Fluoride is incorporated into teeth in a similar manner to its incorporation into bone (World Health Organization, 1984). Unlike bone, which can continue to take up fluoride throughout an individual's lifetime, teeth incorporate fluoride only during their period of calcification (up to about age 12 in humans; Drury et al., 1980).

Only very small amounts of fluoride are found in the soft tissues of the body (with levels generally highest in the kidneys; Heifetz and Horowitz, 1986, Hodge and Smith, 1965), and these levels do not increase with age (World Health Organization, 1984; Drury et al., 1980; see also Knaus et al., 1976). Tissue fluoride concentrations are approximately in equilibrium with plasma fluoride concentrations. Sites of ectopic calcification of soft tissues, such as tendons, cartilage, aorta, or placenta, may accumulate fluoride.

4.3. Excretion

Approximately half of the absorbed fluoride is excreted in the urine (World Health Organization, 1984; Drury et al., 1980); this is the major route of fluoride clearance from the blood and from the body. Renal fluoride excretion involves glomerular filtration followed by pH-dependent tubular reabsorption. Reabsorption occurs by nonionic diffusion of HF (see Whitford et al., 1976), and therefore is greater in acidic urine than in alkaline urine (i.e., fluoride removal from the body is greater in alkalosis than in acidosis; see Smith, 1986b; Whitford et al., 1979; Reynolds et al., 1978). Urinary fluoride is an important indicator of fluoride exposure, and it is routinely used to measure occupational fluoride absorption (Jackson and Hammersley, 1981; National Institute for Occupational Safety and Health, 1976; 1975). For the general population, a good correlation exists between urinary fluoride concentrations and fluoride concentrations in drinking water (World Health Organization, 1984). For one group of people drinking low-fluoride water (<0.2 mg/L) and receiving no occupational exposure to fluoride, the average urinary fluoride level was found to be 0.61 mg/L (upper limit, 2.00 mg/L; after correction for a specific gravity for the urine of 1.024, the average fluoride level was 0.74 mg/L and the upper limit was 3.9 mg/L; Massmann, 1981). Urinary fluoride concentrations of 9 mg/L or greater (corresponding to occupational exposure to more than 2.5 mg/m^3 fluoride in the air or to exposure to 8 mg/L fluoride in the drinking water) are associated with a higher incidence of osteosclerosis (Smith and Hodge, 1979). Preshift urinary fluoride levels below 5.3 mg/L have not been associated with osteosclerosis in workers, and a preshift level of 4 mg/L is thought to provide an adequate margin of protection (National Institute for Occupational Safety and Health, 1976; Derryberry et al., 1963; Largent, 1961). Non-occupationally exposed people whose drinking water contains less than 4 mg/L fluoride are also considered not to be at risk of developing osteosclerosis (National Institute for Occupational Safety and Health, 1976). Urinary excretion of fluoride is decreased in cases of renal failure or disfunction, and retention (i.e., bone deposition) of fluoride increases accordingly (Kono et al., 1984a; 1984b; Gerster et al., 1983). People with renal disfunction are therefore at a higher risk of adverse health effects due to fluoride.

Some fluoride is also excreted in the feces, sweat, saliva, and milk (World Health Organization, 1984). Fluoride in the feces is primarily ingested fluoride that was not absorbed, and fluoride excreted into the gastrointestinal tract

does not appear to be a major source of fecal fluoride (Machle and Largent, 1943). That some fluoride can be excreted into the gastrointestinal tract is suggested by the findings of Largent (1961), in which the fecal fluoride content of human volunteers increased (2.5- to 6.7-fold, highest value was 0.700 mg/day) during a period (2 to 4 weeks) of HF inhalation (0.74 to 6.6 mg/m^3), average individual exposures between 1.2 and 3.9 mg/m^3, 6 hours per day). No coincident increase in oral fluoride intake (food or water) was noted which might have accounted for the observations. Sweat can be an important route of fluoride removal in people who are very active or live in hot climates and whose water intake is therefore very high, but normally only very small amounts of fluoride are found in sweat, saliva, or milk. Fluoride concentrations in sweat of 0.3 to 1.8 mg/L were reported in humans ingesting up to 4.0 to 5.0 mg fluoride per day; 2 weeks after termination of the experiment (returning to normal dietary fluoride intake), the measured fluoride in the subjects' sweat was 0.2 to 0.3 mg/L (McClure et al., 1945).[1] Salivary fluoride concentrations are proportional to plasma fluoride concentrations, while the fluoride concentration in human milk is independent of the plasma fluoride level and therefore of maternal fluoride intake (Ekstrand et al., 1981). Observed fluoride levels in human milk are between 2 and 8 µg/L, less than those in most milk substitutes.

5. Mutagenicity and Carcinogenicity

5.1. Mutagenicity

Several authors have suggested the potential mutagenicity of either hydrogen fluoride or sodium fluoride to plants, *Drosophila*, or mammals (see for instance Caspary et al., 1987; Cole et al., 1986; Tsutsui et al., 1984a; 1984b; 1984c; Mohamed, 1977; Voroshilin et al., 1975; 1973; Gerdes, 1971; Gerdes et al., 1971; Mohamed and Kemner, 1969). On the other hand, Leonard et al. (1977) found no increase in chromosome aberrations in the leukocytes of cattle with chronic fluoride poisoning, nor did Voroshilin et al. (1973) in human leukocytes treated *in vitro* with sodium fluoride. Temple and Weinstein (1978) were unable to demonstrate mutagenicity of HF in tomato plants. Martin et al. (1979) found no evidence for increased chromosome aberrations in mice following exposure to sodium fluoride, nor did they find sodium fluoride to be mutagenic in a bacterial (*Salmonella*) mutagenesis assay. A review by the International Agency for Research on Cancer (1982) did not find sodium fluoride mutagenic in *Salmonella* or *Drosophila*, and both the United States Environmental Protection Agency (Federal Register, 1985b) and the National Research Council (Safe Drinking Water Committee, 1977) conclude that the mutagenicity of fluoride to man has not been demonstrated.

Tsutsui et al. (1984a; 1984b; 1984c) found evidence for DNA damage in cultured human or Syrian hamster cells, including both chromosome aberrations and unscheduled DNA synthesis, following treatment with 50 to 400 mg/L sodium fluoride in the extracellular medium. Cole et al. (1986) concluded that at high (and highly toxic) concentrations (up to 500 mg/L), sodium fluoride caused a small increase in mutation frequency in cultured mouse lymphoma cells, mainly as a result of chromosome breakage; at 10 mg/L fluoride in the medium there was no significant effect. Caspary et al. (1987) demonstrated mutagenic effects in mouse lymphoma cells of both sodium fluoride and potassium fluoride, at concentrations in the range of 300 to 700 mg/L. Tsutsui et al. (1984c) point out that genotoxicity of sodium fluoride has been demonstrated in many *in vitro* studies but in very few *in vivo* studies. The fluoride concentrations used to induce genotoxic effects in these experiments (50 to 700 mg/L) are 2,500 to 70,000 times greater than the normal blood fluoride range (10 to 20 µg/L in humans; World Health Organization, 1984; Drury et al., 1980; Smith and Hodge, 1979). A blood fluoride concentration of 80 µg/L (corresponding to a drinking water level of 5.6 mg/L; Drury et al., 1980; Smith and Hodge, 1979) would still be 600 to 6,000 times lower than the concentrations shown to cause chromosome damage.

Martin et al. (1979) studied chromosome aberrations in bone marrow and testis cells of mice exposed to sodium fluoride. They found no evidence for an increased frequency of chromosome aberrations in mice with a fluoride intake of 50 mg/L in the drinking water for several generations or in mice with an intake of 100 mg/L for 6 weeks. Oral doses of sodium fluoride (up to 84 mg/kg) did not induce DNA-strand breaks in the testicular cells of rats, even when plasma fluoride reached (temporary) concentrations of 11 to 12 mg/L at 2 hours after dosing (Skare et al., 1986a); testicular fluoride levels did not exceed 1 mg/L; suggesting that sodium fluoride does not pose a heritable genetic hazard.

Sodium fluoride has been shown to cause a dose-dependent decrease in the amount of DNA replication in cultured WI-38 (human) cells (Skare et al., 1986b). Fluoride ion is known to inhibit many enzymes, and any effects of fluoride on DNA or chromosomes are more likely the result of fluoride inhibition of DNA repair or replication enzymes than of interaction of fluoride with DNA itself (Cole et al., 1986; Skare et al., 1986b).

5.2. Carcinogenicity

No specific epidemiological evidence is available for the evaluation of the potential carcinogenicity to humans of hydrogen fluoride or other inhaled fluorides. Increased rates of cancer have been reported for workers in several occupations involving possible fluoride exposure, including aluminum production, fluorspar mining, and stainless steel pickling (Grandjean et al., 1985; World Health Organization, 1984; Ahlborg et al., 1981; de Villiers and Windish, 1964). However, all these situations involved mixed exposures to several chemicals (e.g., radon in fluorspar mining, polycyclic aromatic hydrocarbons in aluminum production, and metal compounds and irritating acids in the stainless steel pickling house), and fluoride could not be specifically implicated as the cause of the cancers (Grandjean et al., 1985; World Health Organization, 1984; Ahlborg et al., 1981; Drury et al., 1980; de Villiers and Windish, 1964). Correlation has also been demonstrated between cancer rates and industrial pollution from steel mills, which emit fluoride among other things; again, no specific pollutant could be identified as the major cause of the increased cancer rates (Drury et al., 1980).

The possible carcinogenic potential of fluoride in drinking water has been investigated by comparing rates of cancer in areas with artificially or naturally high fluoride levels in drinking water with the corresponding rates in low fluoride areas. The International Agency for Research on Cancer (1982) concluded that when "proper account was taken of the differences among population units, in demographic composition, and in some cases also in their degree of industrialization and other social factors, none of the studies provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality." The National Research Council (Safe Drinking Water Committee, 1977) and the United States Environmental Protection Agency (Federal Register, 1985b) also agree that the available information does not suggest that fluoride in the drinking water has increased the rate of cancer mortality. The United States Environmental Protection Agency (Federal Register, 1985b) states that "there is not enough information to conclude that fluoride presents a cancer risk to humans" but has not officially classified fluoride or hydrogen fluoride with respect to carcinogenicity.

No animal bioassays have been reported on the potential carcinogenicity of inhaled fluorides. The International Agency for Research on Cancer (1982) reviewed tests of sodium fluoride administered orally to mice and found the data insufficient to permit evaluation. Hydrogen fluoride has been suggested as a contributing factor in the production of lung cancer from cigarette smoking (Sutton, 1986), but no specific evidence is available in support of this idea. The available evidence is thought to be inadequate to support or refute a carcinogenic potential for inhalation exposure to fluorides.

6. Developmental and Reproductive Toxicity

Few reports are available concerning women with industrial fluoride exposure (Smith and Hodge, 1979; Hodge and Smith, 1977). The one available epidemiological study of female workers in a superphosphate plant found a higher incidence of gynecological problems (e.g., menstrual irregularities, vaginal and uterine inflammation, toxicosis during pregnancy, untimely discharge of amniotic fluid) in production workers than in the control group of office workers and housewives (Smith and Hodge, 1979; Hodge and Smith, 1977). The production workers were exposed to dust concentrations of 5 to 57 mg/m^3 and fluoride concentrations of 0.3 to 2.8 mg/m^3. The menstrual irregularities were correlated with dust concentrations, but specific information is not available on possible correlation of gynecological problems with fluoride concentrations in the workplace air or in the urine of the workers. No difference between groups was found in the numbers of pregnancies, miscarriages, or births. No reports of increased incidence of either spontaneous abortions or births of abnormal fetuses have come from communities in the United States with natural fluoride levels of 4 mg/L or more in the drinking water (Smith and Hodge, 1979; Hodge and Smith, 1977). The United States Environmental Protection Agency (Federal Register, 1985b) concludes that there is inadequate evidence to support an association between fluoride in U.S. drinking water and either reproductive or teratogenic effects.

Fluoride is known to cross the placenta and to be deposited in the calcified tissues of the fetus (see Smith et al., 1982; Crissman et al., 1980; Maduska et al., 1980; Rioufol et al., 1980; Krook and Maylin, 1979a; 1979b; Smith and Hodge, 1979). Although fetal exposure is proportional to maternal exposure, the fluoride level in umbilical cord blood increases more slowly than the level in maternal blood; the fetal blood level of fluoride is only about 75 percent of the level in maternal blood. Largent cities a case report of acute fluoride poisoning (ingestion of 50 to 80 g NaF) in a sixteen-year-old girl who was in her 6th week (approximately) of pregnancy (Peters, 1948, cited in Largent, 1961). She was in serious condition at first, but received adequate treatment and recovered within a week; she eventually gave birth to a normal, full-term son. Blood fluoride concentrations were not measured at the time of the poisoning or at the birth of the child.

Excess fluoride in the air, water, or food has caused impaired reproduction in *Drosophila* (Gerdes et al., 1971), mice (Messer et al., 1973), rats (Smith and Hodge, 1979; Hodge and Smith, 1977), and cattle (Crissman et al., 1980; Krook and Maylin, 1979a; 1979b; Safe Drinking Water Committee, 1977). Fluoride doses of 2.5 mg/kg body weight caused cessation of the estrus cycle in rats, and intake of 10 and 150-300 mg/kg caused endocrine malfunction in guinea pigs and rats, respectively (Smith and Hodge, 1979; Hodge and Smith, 1977). Too low a fluoride intake also caused decreased reproductive performance in mice (Messer et al., 1973), but although the essentiality of fluoride to humans has not been satisfactorily demonstrated, fluoride deficiency is not likely to occur in man because of the ubiquity of fluoride in

normal humans diets (Smith, 1986b). Fluoride doses of 1 mg/kg or more have caused bone and tooth malformations in dog, rat, and mouse fetuses (Drury et al., 1980; Hodge and Smith, 1977), and embryo and fetal toxicity from high doses of fluoride (3 to 50 mg/kg/day, dependent on species) have been reported in experimental mammals (Smith and Hodge, 1979). If a 50 kg female worker were exposed to 2.5 mg F/m^3 (the maximum permitted under current occupational standards), she would inhale an estimated 25 mg fluoride per day. If all the inhaled fluoride were actually absorbed (which is not the case), she would receive a maximum of 0.5 mg F/kg/day, which is still less than the fluoride doses necessary to cause toxic effects on reproduction or development in experimental animals. Hodge and Smith (1977) estimate that the toxic doses in animals are 10 to 200 times greater than the total occupational fluoride intake of the 50 kg female worker, and they conclude that the occupational standard is adequate to protect the pregnant woman and her fetus. Machle and Kitzmiller (1935) reported that a rabbit exposed to 15.2 mg HF/m^3 (about 6 times the occupational exposure standard) for 309 hours (6-7 hours per day over about 10 weeks) became pregnant during the exposure period and gave birth to 3 apparently normal offspring 13 days after the exposure ended. The human data that is available at this time does not suggest that HF poses a developmental risk.

Some reports have suggested an increased risk of Down's syndrome associated with fluoridated water (Rapaport, 1963; 1959; 1956; cited in World Health Organization, 1984), but the current consensus is that fluoride has no influence on the incidence of Down's syndrome (World Health Organization, 1984; Shepard, 1983; Smith et al., 1982; Drury et al., 1980; Safe Drinking Water Committee, 1977; Hodge and Smith, 1965). One study does suggest that fluoride has some effect, probably beneficial, on fetal growth in humans (see World Health Organization, 1984).

The major developmental risk to humans from fluoride from any source is dental mottling or fluorosis (staining or pitting of the teeth caused by hypomineralization of the enamel; Heifetz and Horowitz, 1986). Fluorosis occurs in individuals receiving excess fluoride during the period of tooth calcification: prior to birth for the deciduous teeth and up to age 12 for the last of the permanent teeth. The discoloration and pitting are the result of a disturbance affecting the formation of the enamel; damage occurs before the eruption of the teeth (World Health Organization, 1984). Fluorosis can occur in the deciduous teeth of a child when the mother's fluoride intake during pregnancy is high (Grandjean, 1982; Smith and Hodge, 1979); most fluorosis occurs in the permanent teeth and is caused by the child's own high fluoride intake. Fluorosis of the deciduous teeth is naturally of lesser concern than fluorosis of the permanent teeth. The severity of dental fluorosis increases with increased fluoride dose; mild fluorosis occurs at fluoride levels of 1.5 to 2 mg/L in the drinking water (World Health Organization, 1984).

The United States Environmental Protection Agency (1986) gives a No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) of 1 and 2 mg/L (1 and 2 ppm) fluoride in the drinking water, respectively, using dental fluorosis as the endpoint. The Agency has established a Reference Dose (RfD) for oral exposure to fluoride of 0.06 mg/kg/day (U.S. Environmental Protection Agency, 1986). This level corresponds to the fluoride intake expected for a 20-kg child if the water fluoride level is 1 mg/L (the NOAEL). Fluoride intake at this level does not cause dental fluorosis in the sensitive population (children), nor does it cause skeletal fluorosis in adults (United States Environmental Protection Agency, 1986). The Agency does, however, consider dental fluorosis to be a cosmetic

effect rather than a health effect (Federal Register, 1985b), and permits (natural) fluoride levels in the drinking water up to 4 mg/L (4 ppm), a level at which fluorosis, but not in its severest form, does occur.

7. Other Toxic Effects

7.1. Acute Toxicity

Acute exposure to hydrogen fluoride, fluorine, or other gaseous fluorides is rare outside of an occupational setting, although some solutions containing hydrofluoric acid (usually less than 20 percent) are available to the public (Jordan, 1982). The toxicity of some gaseous fluorine compounds decreases in the following order: F_2O, F_2, HF, BF_3, and H_2SiF_6 (World Health Organization, 1984); these compounds can severely damage the skin and respiratory tract of individuals exposed to them. Hydrogen fluoride can be detected by smell at concentrations of less than 1 mg/m^3 (Amoore and Hautala, 1983), and no health effects are observed at 2.6 mg/m^3, but irritation of eyes and respiratory passages is noticed in less than 10 minutes at 26 mg/m^3 or at 13.33 mg/m^3 if exposure is longer than 10 minutes (Just and Emler, 1984; Just, 1984). The Immediately Dangerous to Life or Health (IDLH) level is 16.4 mg/m^3 (20 ppm; Sittig, 1985). [The IDLH level is "the maximum level from which one could escape within 30 minutes without any escape-impairing symptoms or any irreversible health effects" (Just and Emler, 1984).] Machle et al. (1934) reported that the highest concentration of HF tolerated by human volunteers for more than 1 minute was 100 mg/m^3; at this level conjunctival and respiratory irritation was marked, the taste of the gas pronounced, and definite smarting of the skin noted. Irritation and taste were noted also at 50 mg/m^3. There was discomfort at 26 mg/m^3, but the atmosphere could be tolerated for several minutes (Machle et al., 1934). Williams (1942) reported irritation and a runny nose (with occasional bloody discharge after 20 minutes) at concentrations above 10 mg/m^3. Fluorine gas causes almost immediate nasal and eye irritation at a concentration of 25 to 40 mg/m^3 and is intolerable at 40 mg/m^3 (Just and Emler, 1984); the IDLH level is 50 mg/m^3 (25 ppm; Sittig, 1985). Symptoms of HF and F_2 inhalation are similar and include irritation, coughing, and choking followed eventually by symptoms of pulmonary edema (World Health Organization, 1984). Death from hemorrhagic pulmonary edema and destruction of lung tissue may occur (Braun et al., 1984; Gosselin et al., 1984; Kleinfeld, 1965; Mayer and Guelich, 1963). Most available case reports of HF inhalation describe death from pulmonary edema or cardiac and respiratory failure, and no information on long-term pulmonary damage in patients surviving acute HF inhalation is available. In a case of inhalation exposure to mixed hydrofluoric and sulfuric acid, described by Braun et al. (1984), the surviving patient exhibited no obvious pulmonary impairment, but he did continue to have upper respiratory tract problems (hoarseness, coughing, pain, nose bleeds) one year after the exposure.

Machle et al. (1934) reported that exposure to 1,000 to 1,500 mg HF/m^3 for 5 minutes produced death in a significant proportion of rabbits and guinea pigs. Damage to liver, kidney, and lungs was observed in animals exposed to as little as 24.5 mg HF/m^3 (41 hours total exposure, 6 hours/day, autopsied 18 hours post-exposure; no deaths occurred in animals with similar exposure

observed for 1 year following exposure; Machle and Kitzmiller, 1935; Machle et al., 1934). Rosenholtz et al. (1963) reported LC_{50} (lethal concentration for 50 percent of the exposed population) values for rats of 4,060, 2,200, 1,670, and 1,070 mg HF/m^3 for 5, 15, 30, and 60 minutes, respectively, and for guinea pigs of 3,540 mg/m^3 for 15 minutes. Inhalation of 25 mg/m^3 HF for 166 hours total produced 100 percent mortality in rats and mice, but no mortality in guinea pigs, rats, or dogs (Hodge and Smith, 1965). No deaths occurred in any species at 7.2 mg HF/m^3. Exposure to fluorine (F_2) at concentrations as low as 315 mg/m^3 for 3 hours killed all exposed animals (several species) within 14 days. At lower concentrations, guinea pigs appeared to be less susceptible than rats, mice, and rabbits. For 170 hours exposure to 25 mg/m^3 F_2, both rats and guinea pigs exhibited 50 percent mortality (Hodge and Smith, 1965; Stokinger, 1949).

LC_{50} values for mice and rats (without any attempt to estimate human values) have been reported by Vernot et al. (1977) and MacEwen and Vernot (1971). For a 5 minute exposure to HF gas and a 7 day observation period, LC_{50} values of 5,120 mg/m^3 (6,247 ppm; 95% confidence limits of 4,789 and 8,149 ppm) and 14,900 mg/m^3 (18,200 ppm; 95% confidence limits of 15,965 and 20,748 ppm) were obtained for mice and rats, respectively (MacEwen and Vernot, 1971). For a 60 minute exposure, the LC_{50} values for mice and rats, respectively, were 374 mg/m^3 (456 ppm; 95% confidence limits of 426 and 489 ppm) and 792 mg/m^3 (966 ppm; 95% confidence limits of 785 and 1,190 ppm) (Vernot et al., 1977). MacEwen and Vernot report that, following a 5 minute exposure to HF, most of the exposed animals experienced pulmonary edema of varying severity, and pulmonary hemorrhage was a common finding in animals which died during or shortly after exposure to HF concentrations above the LC_{50} value. The available LC values for HF inhalation are summarized in Table 7-1.

Contact of HF or hydrofluoric acid with the skin results in deep, severe burns (Gosselin et al., 1984; World Health Organization, 1984; Mackison et al., 1981; Stokinger, 1981; Drury et al., 1980; Jordan, 1982; Loriot et al., 1981; Greendyke and Hodge, 1964). Fluorine causes thermal burns on the skin (from reaction with the skin) rather than the deep necrosis characteristic of HF burns (World Health Organization, 1984). Solutions of less than 60 percent hydrofluoric acid probably do not pose an inhalation hazard, but skin burns can occur even from low concentrations of hydrofluoric acid (Jordan, 1982). Burns from solutions of less than 20 percent HF may not be noticed for up to 24 hours following skin contact, while solutions greater than 50 percent HF cause immediate pain and tissue damage. Death from systemic fluoride poisoning may occur from HF absorbed via the lungs or the skin (Gosselin et al., 1984; Kono et al., 1982; Tepperman, 1980; Burke et al., 1973). Derelanko et al. (1985) found that dilute (2 percent) concentrations of HF were corrosive to rabbit skin following exposures as short as 5 minutes and that significant absorption of fluoride occurred through the skin. Serum fluoride levels were elevated by 3-fold and 5- to 6-fold following exposure to 2 percent HF for 1 and 4 hours, respectively, and were still significantly elevated 48 hours post-exposure. In rats, systemic fluoride poisoning and death occurred following exposure of 1.7 percent of the body surface to 50 percent HF for 5 minutes (Kono et al., 1982; inhalation of HF by the test animals was prevented). The mortality rate was about 80 percent within 24 hours of treatment. In animals dying within 4 hours of treatment, serum fluoride levels varied from about 80 to 200 times the control level, while serum ionic calcium levels were one-third to one-fiftieth of the control level. Tepperman (1980) and Burke et al. (1973)

Table 7-1. Summary of Lethal Concentration (LC) Estimates for HF Inhalation

LC Level	Concentration mg/m³	Tim min	Concentration x Time mg/m³ x min	Type of Data	Source
LC_{50}	5,120	5[a]	25,600	mouse	MacEwen and Vernot (1971)
	14,900	5[a]	74,500	rat	
LC_{50}	374	60	22,440	mouse	Vernot et al. (1977)
	792	60	47,500	rat	
LC_{100}	148	360	53,280	rat	Morris and Smith (1982)
LC_{100}	105,000	0.5	52,500	estimate for human[b]	Just (1984); Just and Elmer (1984)
	26,000	2			
	10,500	5			
	5,250	10	52,000	estimate for human[b]	
	877	60			
			52,500	estimate for human[b]	
			52,500	estimate for human[b]	
			52,620	estimate for human[b]	

[a]LC values determined for 5 minute exposure, 7 day observation for mortality.
[b]Estimated directly from animal (rat) data without any adjustment.

report cases of fatal or near fatal systemic poisoning in humans following HF burns of only 2.5 percent of the body surface.

Ingested fluorides (sodium fluoride, for instance) are lethal at a dose of 32 to 64 mg fluoride per kg body weight, or about 2.2 to 4.5 g for an adult (Heifetz and Horowitz, 1986; Drury et al., 1980). This corresponds to a dose of 5 to 10 g (70 to 140 mg/kg) of NaF (Heifetz and Horowitz, 1986; Gosselin et al., 1984; World Health Organization, 1984; Drury et al., 1980). This is in keeping with the findings of Lu et al. (1965) of acute lethal doses of fluoride, administered by intravenous infusion at 1 mg/kg/min, of 26.6, 60.0, and 65.8 mg/kg for squirrel monkeys, albino rats, and Rhesus monkeys, respectively. An acute dose of 8 to 16 mg fluoride per kg body weight can be safely tolerated by humans (Heifetz and Horowitz, 1986). The toxicity of specific fluoride compounds varies primarily with their ease of absorption (Drury et al., 1980). Symptoms of acute toxicity following the ingestion of fluoride include nausea and vomiting, caused by local irritation of the gastrointestinal tract (Heifetz and Horowitz, 1986). High doses result in systemic poisoning, with symptoms including convulsions and cardiac arrhythmias (Heifetz and Horowitz, 1986; Baltazar et al., 1980; Abukurah et al., 1972). One report suggests that pulmonary damage due to inhibition of surfactant synthesis may also result from systemic fluoride poisoning, even if the fluoride was not inhaled (Gaugl and Wooldridge, 1983). Death from acute fluoride poisoning, whether from HF inhalation or burns or from ingestion of fluoride salts, is usually from cardiac or respiratory failure and generally occurs within 24 hours (Heifetz and Horowitz, 1986; Stokinger, 1981).

Serum fluoride concentrations of 3 to 15.5 mg/L have been associated with fatal cases of fluoride poisoning, both from oral ingestion of fluorides and from skin burns or inhalation of HF (Gosselin et al., 1984; Tepperman, 1980; Yolken et al., 1976; Hodge and Smith, 1965; Greendyke and Hodge, 1964), although one case has been reported in which the serum fluoride level at autopsy was only 67 µg/L (Braun et al., 1984). Most instances of survival of fluoride or HF poisoning are associated with serum fluoride levels below 3 mg/L (Burke et al., 1973), although one victim of oral fluoride (Na_2SiF_6) poisoning survived despite a serum fluoride of 14 mg/L 6 hours after ingestion of the poison (Yolken et al., 1976). The major route of clearance of excess fluoride from the body following poisoning is the urinary system, and urinary fluoride levels as high as 87 mg/L (3-1/2 hours after the accident) have been reported in survivors (Burke et al., 1973; Yolken et al., 1976). Fluoride concentrations are also increased in soft tissues following fatal intoxication. Levels of 10.6 mg/kg, 4.6 to 11.6 mg/kg, 4.4 to 11.2 mg/kg, and 12.4 to 15.6 mg/kg have been reported in heart, kidney, liver, and lung tissue, respectively, following fatal intake of sodium fluoride (Hodge and Smith, 1965).

7.2. Chronic Toxicity

Chronic exposure to low concentrations (level not specified, but in the context of occupational exposure) of hydrofluoric acid vapors may produce chronic irritation and congestion of the nose, throat, and bronchi (Evans, 1965; cited in Hodge and Smith, 1965). Most other manifestations of chronic fluoride toxicity are dependent solely on the intake of fluoride ion, independent of the source or route of exposure (e.g., HF vs. NaF, airborne vs. waterborne) (Hodge and Smith, 1965). The bones and teeth are the tissues most sensitive to long-term fluoride intake. Dental mottling or fluorosis occurs in humans when fluoride intake is high during the years of tooth calcification to age 12, usually before age 8; see section 6 for discussion). Mild fluorosis can occur with a fluoride intake of about 0.1 mg/kg/day (corresponding to a level of 1.5 to 2 mg/L fluoride in the drinking water); fluorosis (in some cases severe) is common when fluoride intake is 0.2 to 0.35 mg/kg/day (>4 mg/L fluoride in drinking water; see United States Environmental Protection Agency, 1986; Federal Register, 1985a; 1985b; World Health Organization, 1984; Hayes, 1982).

Long-term fluoride intake of 0.2 to 1.0 mg/kg/day or more can result in skeletal fluorosis (Hayes, 1982); this amount corresponds to a level of 4 mg/L or greater in the drinking water or an air concentration of 12 to 26 mg/m^3 (most likely an occupational exposure; Federal Register, 1985a; Hayes, 1982). Kaltreider et al. (1972) reported skeletal fluorosis, with no physical impairment, in a majority of potroom workers in an aluminum plant following exposure to "high concentrations" (2.4 to 6.0 mg/m^3, 8-hr TWA; urinary fluoride ≥8.7 mg/L) for 10 years. Others workers exposed up to 40 years to lower fluoride concentrations (post-shift urinary fluoride ≤4.6 mg/L, pre-shift fluoride ≤1.6 mg/L) did not show any evidence of skeletal fluorosis.

Skeletal fluorosis is defined as an accumulation of fluoride in the skeletal tissues associated with pathological bone formation (World Health Organization, 1984). The earliest observable effect of fluoride deposition in the skeleton is an increased opacity of the bone to X-rays, known as osteosclerosis (Federal Register, 1985a, 1985b; World Health Organization, 1984; Hayes, 1982). Osteosclerosis is first noticeable when the fluoride level reaches 5000 to 6000 mg/kg of dry, fat-free bone (World Health Organization, 1984), a level which corresponds to an intake of 8 mg/L fluoride in the drinking water

for 35 years (Drury et al., 1980). Skeletal fluorosis increases in severity with increased fluoride intake and increased time. Prolonged high fluoride intake can cause "crippling fluorosis," which is characterized by pain, stiffness, irregular bone growth (e.g., exostoses), and calcification of ligaments and tendons. Most cases of crippling fluorosis have occurred in people with a high occupational fluoride exposure (20 to 80 mg/day for 10 to 20 years) or in populations (not in the United States) with drinking water containing 10 to 40 mg/L fluoride (Federal Register, 1985a; 1985b; World Health Organization, 1984; Hayes, 1982; Mackison et al., 1981; see also Schmidt, 1983; Anonymous, 1981a; White, 1980; Smith and Hodge, 1979; Hodge and Smith, 1977). The pain and other symptoms of crippling fluorosis occur as a result of abnormal bone growth, which in turn occurs when the normal metabolism and remodeling of the bone are disrupted by high levels of fluoride. Deposition of fluoride into the bone apatite lattice does not in itself cause harm, nor does the existence of a high fluoride level in the bone. A high bone fluoride level does indicate that fluoride exposure is or has been high, and high fluoride levels will disrupt bone metabolism and can thereby eventually cause crippling.

Similar effects on bones and teeth occur in other mammals subjected to chronic fluoride poisoning, whether from contamination of forage by fluoride emissions from nearby factories (Krook and Maylin, 1979a; 1979b; Gruender, 1972a; 1972b; Oelschlaeger et al., 1972), accidental fluoride contamination of feed (Eckerlin et al., 1986a; 1986b; Parsonson et al., 1975; Hard and Atkinson, 1967a; 1967b; Atkinson and Hard, 1966), or in controlled studies (Grigorenko et al., 1986; Hard and Atkinson, 1967b; Shupe et al., 1963). Severe symptoms can result from extremely high fluoride intake; dairy cattle are probably the most susceptible animals, because of the high calcium turnover and high feed intake associated with lactation (see Eckerlin et al., 1986b).

Machle and Kitzmiller (1935) reported that no externally obvious adverse effects were noted in animals (rabbits, guinea pigs, and Rhesus monkeys) exposed to 15.2 mg/m^3 HF for a total of 309 hours (6 to 7 hours per day over about 10 weeks, followed for up to 8 more months post-exposure). Two guinea pigs sickened and died after 134 and 160 hours exposure. Both of these animals showed liver and lung damage (one had pulmonary hemorrhage), and one had kidney damage. The surviving animals were normal in behavior and appearance but had slower-than-normal growth rates. Some had lower-than-normal erythrocyte counts. These animals upon necropsy exhibited varying degrees of lung, liver, and kidney damage (except the Rhesus monkey, which had kidney damage only). Stokinger (1949) reported pulmonary damage of varying degrees in dogs, rabbits, and rats exposed to 3 to 25 mg/m^3 F_2 for 95 to 176 hours (total, over 3 to 5 weeks) or to 21.1 mg/m^3 HF (7.2 mg/m3 for dogs) for 166 hours (total, over 5 weeks). The dogs also exhibited degenerative testicular changes. Deposition of fluoride inosseous tissues occurred with either F_2 or HF exposure.

Other effects of chronic fluoride exposure in humans have been reported occasionally, including pulmonary effects, renal injury, thyroid injury, anemia, hypersensitivity, and dermatological reactions (Waldbott, 1981; 1980; 1973; 1961; Waldbott and Lee, 1978; McLaren, 1976; Hodge, 1960; Spira, 1944, cited in Princi, 1960). None of these effects has been convincingly established, particularly for fluoride concentrations likely to be encountered by the general public (Federal Register, 1985b; World Health Organization, 1984; Smith and Hodge, 1979; Safe Drinking Water Committee, 1977; Kaltreider et al., 1972; Princi, 1960). The U.S. Environmental Protection Agency (1986) has established an oral Reference Dose (RfD) for fluoride of 0.06 mg/kg/day for children, an intake which corresponds to a water fluoride level of 1 mg/L (1

ppm). Neither dental nor skeletal fluorosis occurs at this level. An inhalation RfD is not available.

7.3. Biochemical Effects

Fluoride toxicity involves at least four major effects (Gosselin et al., 1984): (1) inhibition of enzymes controlling glycolysis or other vital path ways, (2) hypocalcemia resulting from binding or precipitation of calcium by fluoride, (3) cardiovascular collapse caused by hypotension and circulatory shock, and (4) damage to specific organs, primarily the brain and the kidneys.

Fluoride inhibits a number of enzymes, in some cases by complexing with a metal (e.g., Ca^{2+} or Mg^{2+}) associated with the enzyme, in other cases by a direct action of fluoride (as F^- or as undissociated HF) on the enzyme itself (Anonymous, 1985; World Health Organization, 1984; Edwards et al., 1984). Inhibition of many enzymes will occur at high serum fluoride concentrations, at least 300 µg/L (World Health Organization, 1984). Serum fluoride concentrations this high generally occur only with acute high fluoride intake (normal serum fluoride values are much less than 100 g/L, dependent on the fluoride content of the drinking water). Among the results of enzyme inhibition by fluoride are hyperkalemia (increased potassium levels) and metabolic acidosis (Gosselin et al., 1984; World Health Organization, 1984). Fluoride at lower concentrations (about 180 µg/L in serum, still much higher than normal) can activate some other enzymes, most notably adenyl cyclase (World Health Organization, 1984). Fluoride has been shown to affect the metabolism of glucose, lipids and cholesterol, and collagen in mammals, as well as the formation of bones and teeth, and many of these metabolic effects are probably due to the effects of fluoride on the enzymes involved (see for instance Den Besten, 1986; Aitbaev, 1984; Dousset et al., 1984a; 1984b; Drozdz et al., 1984; 1981; Watanabe et al., 1975; serum fluoride levels when reported were at least 50 µg/L).

Hypocalcemia in cases of acute fluoride poisoning will often result in tetany--severe involuntary muscle contractions (Gosselin et al., 1984). Many of the other toxic effects of fluoride (including cardiac arrhythmias and other effects often associated with acute systemic fluoride poisoning) are thought to be caused by hypocalcemia (Heifetz and Horowitz, 1986; Kono et al., 1982; Tepperman, 1980; Abkurah et al., 1972), although the evidence for that is not entirely clear (Gosselin et al., 1984). Most methods of treatment of HF burns or NaF poisoning include immediate replacement of calcium and often also of magnesium (see for instance Bracken et al., 1985; Gosselin et al., 1984; Trevino et al., 1983; Browne, 1982; Carney et al., 1974; Abkurah et al., 1972; Klauder et al., 1955).

Cardiovascular collapse is one of the two most common immediate causes of death in cases of acute fluoride poisoning (Gosselin et al., 1984). The hypotension and circulatory shock which are involved result from a combination of factors such as fluid and electrolyte losses (due to vomiting and diarrhea or intragastric bleeding) and central vasomotor depression. Brain damage from acute fluoride poisoning can cause such symptoms as convulsions, although more commonly lethargy, stupor, and coma are the result. Respiratory failure (the other leading cause of death in fluoride poisoning) is thought to be of central nervous system origin (Gosselin et al., 1984). Renal injury, including transient diabetes insipidus, may also result from acute fluoride poisoning (it is probably not a major concern in cases of chronic fluoride exposure), although renal failure does not appear to be a cause of death (Gosselin et al., 1984). More severe nephrotoxicity, also

including diabetes insipidus, may occur from exposure to fluorine-containing anesthetic agents such as methoxyflurane or enflurane (World Health Organization, 1984).

8. Beneficial Effects

It is generally accepted that fluoride as fluoride ion has a significant cariostatic (cavity-inhibiting) effect (American Academy of Pediatrics, 1986; World Health Organization, 1984; Drury et al., 1980), particularly for individuals who receive it during the years of tooth mineralization (prior to age 6). Fluoride acts systemically in the formation of teeth by being built into the crystal structure of the enamel, making it harder and more resistant to decay; it acts topically on erupted teeth by promoting remineralization (American Academy of Pediatrics, 1986). The acids produced by various oral bacteria contribute to tooth decay by dissolving enamel; fluoride on the tooth surface has a bacteriostatic effect, resulting in a decrease in acid production and ultimately a decrease in tooth decay (Drury et al., 1980).

The most effective way to administer fluoride to the population is via the water supply, and a number of communities throughout the world now have artificially fluoridated municipal water supplies. The typical fluoride level for an artificially fluoridated water source in a temperate climate is 1 mg/L (1 ppm; Safe Drinking Water Committee, 1977); the recommended fluoride level changes with the average temperature of a region, due to differences in expected water consumption (Hayes, 1982). Other means of fluoride delivery include fluoride-containing tablets, drops, toothpastes, and mouthwashes (American Academy of Pediatrics, 1986). A few reports suggest that at least some of the decline in tooth decay attributed to fluoridated water may in fact be due to other causes, such as changes in immune status, changes in dietary patterns, and use of topical fluorides (Diesendorf, 1986; Smith, 1986a; 1986c).

The increased bone density found in individuals with a high long-term fluoride intake suggests a possible use for fluoride in the prevention or treatment of such diseases as osteoporosis, characterized by an accelerated decrease in bone mass and strength (Smith, 1986b; World Health Organization, 1984). Some evidence exists that people living in an area with a high natural level of fluoride in the water (4 to 8 mg/L) have a lower incidence of osteoporosis (World Health Organization, 1984). Medical use of high fluoride doses (50+ mg/day, usually given with calcium and vitamin D supplements; Drury et al., 1980) is still under investigation (see Dambacher et al., 1986; Frey, 1986; Smith, 1986b; World Health Organization, 1984; Drury et al., 1980). In at least some cases, bone density seems to be increased without a concommitant increase in bone strength--bone formation is stimulated by fluoride, and fluoride is incorporated into the bone structure, but the overall bone structure is not entirely normal and is not necessarily stronger (Frey, 1986; Smith, 1986b; see also Dambacher et al., 1986; Snow and Anderson, 1986). Some side effects such as gastrointestinal bleeding (Frey, 1986) or osteoarticular side effects (Dambacher et al., 1986) can occur from treatment with large amounts of fluoride, and severe fluorosis can result if a patient with renal insufficiency is given fluoride for treatment of osteoporosis (Gerster et al., 1983).

Some epidemiological studies have suggested a correlation between increased fluoride levels in drinking water (the high level in one study was 2.57

mg/L) and a decrease in mortality due to heart disease (World Health Organization, 1984; Luoma et al., 1973). The details of the relationship between fluoride and cardiovascular disease remain to be worked out, although one possibility is that fluoride may reduce soft tissue calcification such as atherosclerosis.

The beneficial effects and the adverse effects of fluoride must be weighed in determining the optimal fluoride level in drinking water supplies. The most effective level for the prevention of caries seems to be about 1.0 to 1.2 mg/L; higher amounts (at least 4 to 5 mg/L) may be necessary for the prevention of osteoporosis. Some cases of mild dental fluorosis are found when the water contains 1 to 2 mg/L fluoride; fluorosis is common and occasionally severe at 4 mg/L. Although dental fluorosis is treated as a cosmetic effect and not a health effect, some people do consider it objectionable (Federal Register, 1985b).

Fluoride is usually added to water in the form of sodium fluoride (NaF), sodium fluosilicate (Na_2SiF_6), fluosilicic acid (H_2SiF_6), or ammonium fluosilicate [$(NH_4)_2SiF_6$] (Safe Drinking Water Committee, 1977). Sodium fluoride, stannous fluoride (SnF_2), acidulated phosphate fluoride, and monofluorophosphate are the fluorides most commonly added to dentifrices and mouthwashes (Heifetz and Horowitz, 1986). Sodium fluoride is also the main fluoride used in treatment of osteoporosis (Frey, 1986; Smith, 1986b), although at least one fluorine-containing organic compound, niflumic acid (2-[3-(trifluoromethyl)anilino]nicotinic acid), has been suggested as a possible drug for this use (Meunier et al., 1980). Hydrogen fluoride is not used in these capacities, although it is important as an intermediate in the production of some of these other fluoride compounds.

9. References

Abukurah, A. R.; Moser, A. M., Jr.; Baird, C. L.; Randall, R. E., Jr. Setter, J. G.; Blanke, R. V. (1972) Acute sodium flouride poisoning. JAMA J. Am. Med. Assoc. 222: 816-817.

Ahlborg, G.; Hogstedt, C.; Sundell, L.; Aman, C.-G. (1981) Laryngeal cancer and pickling house vapors. Scand. J. Work Environ. Health 7: 239-240.

Aitbaev, T. Kh. (1984) [Changes in various indicators of lipid metabolism during isolated and combined exposure to hydrogen flouride, sulfur dioxide and hydrogen sulfide in various concentrations]. Gig. Tr. Prof. Zabol. (6): 16-19.

Alary, J.; Bourbon, P.; Balsa, C.; Bonte, J.; Bonte, C. (1981) A field study of the validity of static paper sampling in flouride pollution surveys. Sci. Total Environ. 22: 11-18

American Academy of Pediatrics, Committee on Nutrition. (1986) Flouride supplementation. Pediatrics 77: 758-761.

American Conference of Governmental Industrial Hygienists. (1986) TLV's: threshold limit values for chemical substances in the work environment adopted by ACGIH with intended changes for 1986-87. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Amoore, J. E.; Hautala, E. (1983) Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. JAT J. Appl. Toxicol. 3: 272-290.

Anonymous. (1981a) Chronic flourosis. Br. Med. J. 282: 253-254.

Anonymous. (1981b) Hydroflouric acid. Dangerous Prop. Ind. Mater. Rep. 1(6): 64-66.

Anonymous. (1985) How flouride might damage your health. New Sci. (1445): 20.

Anonymous. (1986) Flouride in food and water. Nutr. Rev. 44: 233-235.

Atkinson, F. F. V.; Hard, G. C. (1966) Chronic flourosis in the guinea-pig. Nature (London) 211: 429-430.

Baltazar, R. F.; Mower, M. M.; Reider, R.; Funk, M.; Salomon, J. (1980) Acute fluoride poisoning leading to fatal hyperkalemia. Chest 78: 660-663.

Barnard, W. R.; Nordstrom, D. K. (1982) Flouride in precipitation - II. Implications for the geochemical cycling of flourine. Atmos. Environ. 16: 105-111.

Bartels, O. G. (1972) An estimate of volcanic contributions to the atmosphere and volcanic gases and sublimates as the source of the radioisotopes ^{10}Be, ^{35}S, ^{32}P, and ^{22}Na. Health Phys. 22: 387-392.

Baxter, P. J.; Stoiber, R. E.; Williams, S. N. (1982) Volcanic gases and health: Masaya Volcano, Nicaragua [letter]. Lancet (8290): 150-151.

Boscak, V. (1978) Screening study on feasibility of standards of performance for hydroflouric acid manufacture. Research Triangle Park, NC: U. S. Environmental Protection Agency, Office of Air Quality Planning and Standards; EPA report no. EPA-450/3-78-109. Available from: NTIS, Springfield, VA; PB-294276.

Bostick, W. D.; McCulla, W. H.; Pickrell, P. W. (1985) Sampling, characterization, and remote sensing of aerosols formed in the atmospheric hydrolysis of uranium hexaflouride. J. Environ. Sci. Health A20: 369-393.

Boublik, T.; Fried, V.; Hala, E. (1984) The vapour pressures of pure substances: selected values of the temperature dependence of the vapour pressures of some pure substances in the normal and low pressure region. 2nd rev. ed. Amsterdam, The Netherlands: Elsevier Scientific Publishing Co., Inc. (Physical sciences data series: v. 17).

Bracken, W. M.; Cuppage, F.; McLaury, R. L.; Kirwin, C.; Klaassen, C. D. (1985) Comparative effectiveness of topical treatments for hydroflouric acid burns. JOM J. Occup. Med. 27: 733-739.

Braun, J.; Stoess, H.; Zober, A. (1984) Intoxication following the inhalation of hydrogen flouride. Arch. Toxicol. 56: 50-54.

Browne, T. D. (1982) Hydroflouric acid skin burns - addendum [letter]. JOM J. Occup. Med. 24: 79.

Burke, W. J.; Hoegg, U. R.; Phillips, R. E. (1973) Systemic flouride poisoning resulting from a flouride skin burn. JOM J. Occup. Med. 15: 39-41.

Carney, S. A.; Hall, M.; Lawrence, J. C.; Ricketts, C. R. (1974) Rationale of the treatment of hydroflouric acid burns. Br. J. Ind. Med. 31: 317-321.

Carpenter, R. (1969) Factors controlling the marine geochemistry of flourine.

Geochim. Cosmochim. Acta 33: 1153-1167.

Caspary, W. J.; Myhr, B.; Bowers, L.; McGregor, D.; Riach, C.; Brown, A. (1987) Mutagenic activity of fluorides in mouse lymphoma cells. Mutat. Res. 187: 165-180.

Chemical Marketing Reporter. (1986) US fertilizer usage seen slipping further with ag export fall. Chem. Mark. Rep. 230(11): 7, 18-19.

Chester, R. O.; Kirkscey, K. A.; Randolph, M. L. (1979) Survey of knowledge of hazards of chemicals potentially associated with the advanced isotope separation processes. Oak Ridge, TN: Oak Ridge National Laboratory; ORNL/TM-6812. Available from: NTIS, Springfield, VA; ORNL/TM-6812.

Code of Federal Regulations. (1985) Subpart Z--toxic and hazardous substances: air contaminants. C. F. R. 29: 1910.1000.

Cole, J.; Muriel, W. J.; Bridges, B. A. (1986) The mutagenicity of sodium flouride to L5178Y [wild-type and TK+/- (3.7.2c)] mouse lymphoma cells. Mutagenesis 1: 157-167.

Collings, G. H., Jr.; Fleming, R. B. L.; May, R. (1951) Absorption and excretion of inhaled fluorides. AMA Arch. Ind. Hyg. Occup. Med. 4: 585-590.

Crissman, J. W.; Maylin, G. A.; Krook, L. (1980) New York State and U. S. Federal flouride pollution standards do not protect cattle health. Cornell Vet. 70: 183-192.

Dambacher, M. A.; Ittner, J.; Ruegsegger, P. (1986) Long-term fluoride therapy of postmenopausal osteoporosis. Bone 7: 199-205.

de Villiers, A. J.; Windish, J. P. (1964) Lung cancer in a fluorspar mining community: I. radiation, dust, and mortality experience. Br. J. Ind. Med. 21: 94-109.

Den Besten, P. K. (1986) Effects of flouride on protein secretion and removal during enamel development in the rat. J. Dent. Res. 65: 1272-1277.

Derelanko, M. J.; Gad, S. C.; Gavigan, F.; Dunn, B. J. (1985) Acute dermal toxicity of dilute hydroflouric acid. J. Toxicol. Cutaneous Ocul. Toxicol. 4: 73-85.

Derryberry, O. M.; Bartholomew, M. D.; Fleming, R. B. L. (1963) Fluoride exposure and worker health: the health status of workers in a fertilizer manufacturing plant in relation to fluoride exposure. Arch. Environ. Health 6: 503-511.

Diesendorf, M. (1986) The mystery of declining tooth decay. Nature (London) 322: 125-129.

Dousset, J. C.; Feliste, R.; Rioufol, C.; Levy, P.; Bourbon, P. (1984a) Influence de l'acide flourhydrique inhale sur le cholesterol plasmatique de cobayes avec ou sans carence en vitamine C [Influence of inhaled hydrogen

flouride on plasma cholesterol levels in normal guinea-pigs and guinea-pigs with vitamin C deficiency]. Ann. Pharm. Fr. 42: 425-429.

Dousset, J. C.; Rioufol, C.; Feliste, R.; Levy, P.; Bourbon, P. (1984b) Effects of inhaled HF on lipid metabolism in guinea pigs. Fundam. Appl. Toxicol. 4: 618-623.

Drozdz, M.; Kucharz, E.; Grucka-Mamczar, E. (1981) Studies on the influence of flouride compounds upon connective tissue metabolism in growing rats: I. effect of hydrofluoride on collagen metabolism. Toxicol. Eur. Res. 3: 237-241.

Drozdz, M.; Kucharz, E.; Stawiarska, B. (1984) Studies on the influence of fluoride compounds upon connective tissue metabolism in growing rats: II.-effect of oral administration of sodium fluoride with and without simultaneous exposure to hydroxyfluoride on collagen metabolism. J. Toxicol. Med. 4: 151-157.

Drury, J. S.; Ensminger, J. T.; Hammons, A. S.; Holleman, J. W.; Lewis, E. B.; Preston, E. L.; Shriner, C. R.; Towill, L. E. (1980) Reviews of the environmental effects of pollutants: IX. fluoride. Cincinnati, OH: U. S. Environmental Protection Agency, Health Effects Research Laboratory; report no. ORNL/EIS-85 and EPA-600/1-78-050. Available from: NTIS, Springfield, VA; ORNL/EIS-85.

Eckerlin, R. H.; Krook, L.; Maylin, G. A.; Carmichael, D. (1986a) Toxic effects of food-borne fluoride in silver foxes. Cornell Vet. 76: 395-402.

Eckerlin, R. H.; Maylin, G. A.; Krook, L. (1986b) Milk production of cows fed fluoride contaminated commercial feed. Cornell Vet. 76: 403-414.

Edwards, S. L.; Poulos, T. L.; Kraut, J. (1984) The crystal structure of fluoride-inhibited cytochrome c peroxidase. J. Biol. Chem. 259: 12984-12988.

Ekstrand, J.; Boreus, L. O.; de Chateau, P. (1981) No evidence of transfer of fluoride from plasma to breast milk. Br. Med. J. 283: 761-762.

Evans, E. E. (1965) [Written communication to Hodge, H. C. and Smith, F. A.].

Federal Register. (1985a) National primary drinking water regulations; fluoride [proposed rulemaking]. F. R. 50 (May 14): 20164-20175.

Federal Register. (1985b) National primary drinking water regulations; fluoride [final rule]. F. R. 50 (November 14): 47142-47171.

Forbes, G. B.; Taves, D. R.; Smith, F. A.; Kilpper, R. W. (1978) Bone mineral turnover in a patient with osteogenesis imperfecta estimated by fluoride excretion. Calcif. Tissue Res. 25: 283-287.

Frey, H. (1986) Fluoride in the treatment of osteoporosis [editorial]. Acta Med. Scand. 220: 193-194.

Gall, J. F. (1980) Fluorine compounds, inorganic: hydrogen. In: Kirk-Othmer encyclopedia of chemical technology: v. 10. 3rd ed. New York, NY: John Wiley & Sons; pp. 733-753.

Gaugl, J. F.; Wooldridge, B. (1983) Cardiopulmonary response to sodium fluoride infusion in the dog. J. Toxicol. Environ. Health 11: 765-782.

Gerdes, R. A. (1971) The influence of atmospheric hydrogen fluoride on the frequency of sex-linked recessive lethals and sterility in *Drosophila melanogaster*. Fluoride Q. Rep. 4: 25-29.

Gerdes, R. A.; Smith, J. D.; Applegate, H. G. (1971) The effects of atmospheric hydrogen fluoride upon *Drosophila melanogaster*--II fecundity, hatchability and fertility. Atmos. Environ. 5: 117-122.

Gerster, J. C.; Charhon, S. A.; Jaeger, P.; Boivin, G.; Briancon, D.; Rostan, A.; Baud, C. A.; Meunier, P. J. (1983) Bilateral fractures of femoral neck in patients with moderate renal failure receiving fluoride for spinal osteoporosis. Br. Med. J. 287: 723-725.

Gosselin, R. E.; Smith, R. P.; Hodge, H. C.; Braddock, J. E. (1984) Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams & Wilkins; pp. III-185--III-193.

Grandjean, P. (1982) Classical syndromes in occupational medicine. Occupational fluorosis through 50 years: clinical and epidemiological experiences. Am. J. Ind. Med. 3: 227-236.

Grandjean, P.; Juel, K.; Jensen, O. M. (1985) Mortality and cancer morbidity after heavy occupational fluoride exposure. Am. J. Epidemiol. 121: 57-64.

Greendyke, R. M.; Hodge, H. C. (1964) Accidental death due to hydrofluoric acid. J. Forensic Sci. 9: 383-390.

Grigorenko, V. K.; Bachinsky, P. P.; Bogdan, S. S. (1986) Changes in mechanical properties and chemical composition of osseous tissues of white rats during excessive income of fluoride into organism. Fiziol. Zh. 32: 340-344.

Gruender, H.-D. (1972a) Fluorimmissionswirkungen auf Rinder. Zusammenfassende Darstellung der Ergebnisse mehrjaehriger Untersuchungen im Bereich einer Flussaeure- und einer Aluminiumfabrik [Effects of fluorine emission on cattle. Comprehensive results of studies conducted over several years in the neighborhood of a hydrofluoric acid and aluminum factory]. Zentralbl. Veterinaermed. Reihe A 19: 229-264.

Gruender, H.-D. (1972b) Fluorimmissionswirkungen auf Rinder. Zusammenfassende Darstellung der Ergebnisse mehrjaehriger Untersuchungen im Bereich einer Flussaeure- und einer Aluminiumfabrik [Effects of fluorine emission on cattle. Comprehensive results of studies

conducted over several years in the neighborhood of a hydrofluoric acid and aluminum factory]. Zentralbl. Veterinaermed. Reihe A 19: 265-309.

Gutknecht, J.; Walter, A. (1981) Hydrofluoric and nitric acid transport through lipid bilayer membranes. Biochim. Biophys. Acta 664: 153-156.

Hansch, C. H.; Leo, A. (1979) Substituent constants for correlation analysis in chemistry and biology. New York, NY: John Wiley & Sons; p. 172.

Hard, G. C.; Atkinson, F. F. V. (1967a) "Slobbers" in laboratory guinea-pigs as a form of chronic fluorosis. J. Pathol. Bacteriol. 94: 95-102.

Hard, G. C.; Atkinson, F. F. V. (1967b) The aetiology of "slobbers" (chronic fluorosis) in the guinea-pig. J. Pathol. Bacteriol. 94: 103-112.

Hayes, W. J., Jr. (1982) Pesticides studied in man. Baltimore, MD: Williams & Wilkins; pp. 56-60.

Heifetz, S. B.; Horowitz, H. S. (1986) Amounts of fluoride in self-administered dental products: safety considerations for children. Pediatrics 77: 876-882.

Hilado, C. J.; Cumming, H. J. (1978) Short-term LC_{50} values: an update on available information. Fire Technol. 14: 46-50.

Hilado, C. J.; Furst, A. (1976) Short-term LC_{50} values and fire toxicity. Proc. West. Pharmacol. Soc. 19: 405-407.

Hodge, H. C. (1960) Notes on the effects of fluoride deposition on body tissues. AMA Arch. Ind. Health 21: 350-352.

Hodge, H. C.; Smith, F. A. (1965) Fluorine chemistry: v. 4. Simons, J. H., ed. New York, NY: Academic Press.

Hodge, H. C.; Smith, F. A. (1972) Fluorides. In: Lee, D. H. K., ed. Metallic contaminants and human health. New York, NY: Academic Press; pp. 163-187. (Fogerty International Center proceedings: no. 9).

Hodge, H. C.; Smith, F. A. (1977) Occupational fluoride exposure. JOM J. Occup. Med. 19: 12-39.

International Agency for Research on Cancer. (1982) Inorganic fluorides used in drinking-water and dental preparations. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: v. 27, some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking-water and dental preparations. Lyon, France: World Health Organization; pp. 237-303.

International Labour Office. (1984) Occupational exposure limits for airborne toxic substances: a tabular compilation of values from selected countries. 2nd rev. ed. Geneva, Switzerland: International Labour Office; pp. 9-10, 118-119, 128-129, 242m. (Occupational safety and health series: no. 37).

Jackson, J. R.; Hammersley, H. (1981) Biological monitoring for occupational fluoride absorption. Fluoride 14: 75-86.

Jahr, J. (1983) Nordisk ekspertgruppe for dokumentasjon av grenseverdier 41. Hydrogenfluorid [Hydrogen fluoride: Nordic expert group for documentation of occupational exposure limits]. Arb. Halsa 17.

Jordan, J. K. (1982) Hydrofluoric acid: a new corrosive poison? In: Proceedings of the 1982 international congress of clinical toxicology and the second annual meeting of clinical toxicology; August; Snowmass, CO. Vet. Hum. Toxicol. 24(suppl.): 40-42.

Just, R. A. (1984) Report on toxicological studies concerning exposures to UF_6 and UF_6 hydrolysis products. Oak Ridge, TN: U. S. Department of Energy, Oak Ridge Gaseous Diffusion Plant; report no. K/D-5573-REV.1. Available from: NTIS, Springfield, VA; DE84015354.

Just, R. A.; Emler, V. S. (1984) Generic report on health effects for the U. S. gaseous diffusion plants. Oak Ridge, TN: U. S. Department of Energy, Oak Ridge Gaseous Diffusion Plant; report no. K/D-5050-SEC.8-PT.1. Available from: NTIS, Springfield, VA; DE84014303.

Kaltreider, N. L.; Elder, M. J.; Cralley, L. V.; Colwell, M. O. (1972) Health survey of aluminum workers with special reference to fluoride exposure. JOM J. Occup. Med. 14: 531-541.

Klauder, J. V.; Shelanski, L.; Gabriel, K. (1955) Industrial uses of compounds of fluorine and oxalic acid: cutaneous reaction and calcium therapy. AMA Arch. Ind. Health 12: 412-419.

Kleinfeld, M. (1965) Acute pulmonary edema of chemical origin. Arch. Environ. Health 10: 942-946.

Knaus, R. M.; Dost, F. N.; Johnson, D. E.; Wang, C. H. (1976) Fluoride distribution in rats during and after continuous infusion of $Na^{18}F$. Toxicol. Appl. Pharmacol. 38: 335-343.

Kono, K.; Yoshida, Y.; Harada, A.; Watanabe, M.; Hirota, T.; Tanimura, Y.; Shibuya, Y. (1982) An experimental study on the biochemical consequences of hydrofluoric acid burns. Bull. Osaka Med. Sch. 28: 124-133.

Kono, K.; Yoshida, Y.; Harada, A. (1984a) Urinary excretion of fluoride in chronic renal failure and hydrofluoric acid workers. Collect. Med. Leg. Toxicol. Med. 125 (pt. 1): 91-99.

Kono, K.; Yoshida, Y.; Watanabe, M.; Tanimura, Y.; Hirota, T. (1984b) Urinary fluoride excretion in fluoride exposed workers with diminished renal function. Ind. Health 22: 33-40.

Krook, L.; Maylin, G. A. (1979a) Industrial fluoride pollution. In: Hemphill, D. D., ed. Trace substances in environmental health-XIII: [proceedings of

University of Missouri's 13th annual conference on trace substances in environmental health]; June; Columbia, MO. Columbia, MO: University of Missouri-Columbia; pp. 262-270.

Krook, L.; Maylin, G. A. (1979b) Industrial fluoride pollution: chronic fluoride poisoning in Cornwall Island cattle. Cornell Vet. 69 (suppl. 8).

Largent, E. J. (1952) Rates of elimination of fluoride stored in the tissues of man. AMA Arch. Ind. Hyg. Occup. Med. 6: 37-42.

Largent, E. J. (1961) Fluorosis: the health aspects of fluorine compounds. Columbus, OH: Ohio State University Press.

Leonard, A.; Deknudt, Gh.; Decat, G.; Leonard, E. D. (1977) Cytogenetic investigations on leucocytes of cattle intoxicated with fluoride. Toxicology 7: 239-242.

Levenson, N. M.; March, A. H.; Bakker, J.; Kamatari, O. (1982) Fluorine minerals and inorganic fluorine compounds. In: Chemical economics handbook. Menlo Park, CA: SRI International; pp. 739.1000 A-739.1002 U.

Loriot, J.; Penneau, D.; Bailly, C.; Lahitete, F.; Domont, A.; Proteau, J. (1981) A propos de la pathalogie professionnelle liee a l'acide fluor hydrique [On occupational pathology due to hydrofluoric acid]. Arch. Mal. Prof. Med. Trav. Secur. Soc. 42: 126-128.

Lu, F. C.; Grewal, R. S.; Rice, W. B.; Graham, R. C. B.; Allmark, M. G. (1965) Acute toxicity of sodium fluoride for Rhesus monkeys and other laboratory animals. Acta Pharmacol. Toxicol. 22: 99-106.

MacEwen, J. D.; Vernot, E. H. (1971) Toxic hazards research unit annual technical report: 1971. Wright-Patterson Air Force Base, OH: Aerospace Medical Research Laboratory; AMRL report no. AMRL-TR-71-83. Available from: NTIS, Springfield, VA; AD-734543.

Machle, W.; Kitzmiller, K. (1935) The effects of the inhalation of hydrogen fluoride. II. The response following exposure to low concentration. J. Ind. Hyg. 17: 223-229.

Machle, W.; Largent, E. J. (1943) The absorption and excretion of fluoride: II. the metabolism at high levels of intake. J. Ind. Hyg. Toxicol. 25: 112-123.

Machle, W.; Thamann, F.; Kitzmiller, K.; Cholak, J. (1934) The effects of the inhalation of hydrogen fluoride. I. The response following exposure to high concentrations. J. Ind. Hyg. 16: 129-145.

Mackison, F. W.; Stricoff, R. S.; Partridge, L. J., Jr., eds. (1981) NIOSH/OSHA occupational health guidelines for chemical hazards. Washington, DC: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health; DHHS (NIOSH) publication no. 81-123. Available from: GPO, Washington, DC; S/N 017-033-00337-8.

Maduska, A. L.; Ahokas, R. A.; Anderson, G. D.; Lipshitz, J.; Morrison, J. C. (1980) Placental transfer of intravenous fluoride in the pregnant ewe. Am. J. Obstet. Gynecol. 136: 84-86.

Mahadevan, T. M.; Meenakshy, V.; Mishra, U. C. (1986) Fluoride cycling in nature through precipitation. Atmos. Environ. 20: 1745-1749.

Mankin, W. G.; Coffey, M. T. (1983) Latitudinal distributions and temporal changes of stratospheric HCl and HF. JGR J. Geophys. Res. 88(C15): 10776-10784.

Martin Marietta Energy Systems, Incorporated. (1985) Environmental monitoring report: United States Department of Energy Paducah gaseous diffusion plant, calender year 1984. Paducah, KY: U. S. Department of Energy, Paducah Gaseous Diffusion Plant; report no. KY-747. Available from: NTIS, Springfield, VA; DE85014027/XAB.

Martin, A. E.; Jones, C. M. (1971) Some medical considerations regarding atmospheric fluorides. HSHMA Health Rep. 86: 752.

Martin, G. R.; Brown, K. S.; Matheson, D. W.; Lebowitz, H.; Singer, L.; Ophaug, R. (1979) Lack of cytogenetic effects in mice or mutations in Salmonella receiving sodium fluoride. Mutat. Res. 66: 159-167.

Massmann, W. (1981) Reference values of renal excretion of fluoride. J. Clin. Chem. Clin. Biochem. 19: 1039-1041.

Mayer, L.; Guelich, J. (1963) Hydrogen fluoride (HF) inhalation and burns. Arch. Environ. Health 7: 445-447.

McClure, F. J.; Mitchell, H. H.; Hamilton, T. S.; Kinser, C. A. (1945) Balances of fluorine ingested from various sources in food and water by five young men: excretion of fluorine through the skin. J. Ind. Hyg. Toxicol. 27: 159-170.

McLaren, J. R. (1976) Possible effects of fluorides on the thyroid. Fluoride 9: 105-116.

MEDLARS II, Medical Literature Analysis and Retrieval System [data base]. (1986) [Printout of record 546, hydrogen fluoride, from the Hazardous Substances Databank and CAS no. 7664-39-3, hydrogen fluoride, from the Registry of Toxic Effects of Chemical Substances as of September 11]. Bethesda, MD: U. S. Department of Health and Human Services, National Library of Medicine. Disc; EBCDIC. Available for inspection at: U. S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Messer, H. H.; Armstrong, W. D.; Singer, L. (1973) Influence of fluoride intake on reproduction in mice. J. Nutr. 103: 1319-1326.

Meunier, P. J.; Courpron, P.; Smoller, J. S.; Briancon, D. (1980) Niflumic acid-induced skeletal fluorosis: iatrogenic disease or therapeutic perspective for osteoporosis? Clin. Orthop. Relat. Res. (148): 304-309.

Misenheimer, D. C.; Battye, R. E.; Clowers, M. R.; Werner, A. S. (1985) Hydrogen chloride and hydrogen fluoride: emission factors for the NAPAP emission inventory. Research Triangle Park, NC: U. S. Environmental Protection Agency, Air and Energy Engineering Research Laboratory; EPA report no. EPA-600/7-85/041. Available from: NTIS, Springfield, VA; PB86-134020.

Mohamed, A. H. (1977) Cytogenetic effects,of hydrogen fluoride gas on maize. Fluoride 10: 157-164.

Mohamed A. H.; Kemner, P. A. (1969) Cytogenetic effects of hydrogen fluoride on *Drosophila melanogaster* [abstract]. Genetics 61: S41-S42.

Morris, J. B.; Smith, F. A. (1982) Regional deposition and absorption of inhaled hydrogen fluoride in the rat. Toxicol. Appl. Pharmacol. 62: 81-89.

Morris, J. B.; Smith, F. A. (1983) Identification of two forms of fluorine in tissues of rats inhaling hydrogen fluoride. Toxicol. Appl. Pharmacol. 71: 383-390.

Murphy, G. A. (1986) Selected safety-related events reported in January, February, and March 1986. Nucl. Saf. 27: 394-396.

National Institute for Occupational Safety and Health. (1975) Criteria for a recommended standard...occupational exposure to inorganic fluorides. Washington, DC: U. S. Department of Health, Education, and Welfare, Center for Disease Control; publication no. DHEW/NIOSH-76-103. Available from: NTIS, Springfield, VA; PB-246692/8.

National Institute for Occupational Safety and Health. (1976) Criteria for a recommended standard...occupational exposure to hydrogen fluoride. Washington, DC: U. S. Department of Health, Education, and Welfare, Center for Disease Control; publication no. DHEW/PUB/NIOSH-76-143. Available from: NTIS, Springfield, VA; PB81-226516.

National Research Council. (1971) Fluorides. Washington, DC: National Academy of Sciences.

National Research Council. (1974) Effects of fluorides in animals. Washington, DC: National Academy of Sciences.

Oelschlaeger, W.; Feyler, L.; Schwarz, E. (1972) Fluorgehalte in Weichgeweben, Blut und Milch von Wiederkaeuern ausserhalb und in Fluoremissionsgebieten [Fluorine content in the soft tissues, blood and milk of ruminants outside and inside fluorine emission areas]. Zentralbl. Veterinaermed. Reihe A 19: 743-752.

Ophaug, R. H.; Singer, L. (1977) Influence of variations in fluoride intake on the ionic and bound fractions of plasma and muscle fluoride (39736). Proc. Soc. Exp. Biol. Med. 155: 23-26.

Parsonson, I. M.; Carter, P. D.; Cruickshanks, J. (1975) Chronic fluorosis in laboratory guinea pigs. Aust. Vet. J. 51: 362-363.

Peters, J. H. (1948) Therapy of acute fluoride poisoning. Am. J. Med. Sci. 216: 278.

Princi, F. (1960) Fluorides: a critical review. III. The effects on man of the absorption of fluoride. JOM J. Occup. Med. 2: 92-99.

Rapaport, I. (1956) Contribution a l'etude de mongolisme. Role pathogenique du fluor. Bull. Acad. Natl. Med. 140: 529-531. [As cited in: World Health Organization, 1984.]

Rapaport, I. (1959) Nouvelles recherches sur le mongolisme. A propos du role pathogenique du fluor. Bull. Acad. Natl. Med. 143: 367-370. [As cited in: World Health Organization, 1984.]

Rapaport, I. (1963) Oligophrenie mongolienne et caries dentaires. Rev. Stomato. 46: 207. [As cited in: World Health Organization, 1984.]

Reynolds, K. E.; Whitford, G. M.; Pashley, D. H. (1978) Acute fluoride toxicity: the influence of acid-base status. Toxicol. Appl. Pharmacol. 45: 415-427.

Rioufol, C.; Poey, J.; Bourbon, P. (1980) Etude de la fixation du fluor au niveau des tissus calcifies chez le Cobaye apres 18 mois d'exposition a une atmosphere renfermant 100 a 150 g d'acide fluorhydrique par metre cube [Fluorine uptake by calcified tissues in the guinea pig after 18 months exposure to an atmosphere containing 100 to 150 mcg hydrofluoric acid per cubic meter]. C. R. Hebd. Seances Acad. Sci. Ser. D 290: 215-217.

Rioufol, C.; Bourbon, P.; Vrancken, L. (1983) Comparative study of fluoride elimination from guinea pig bone after long and short-term exposure to hydrogen fluoride. Fluoride 16: 162-168.

Rosenholtz, M. J.; Carson, T. R.; Weeks, M. H.; Wilinski, F.; Ford, D. F.; Oberst, F. W. (1963) A toxicopathologic study in animals after brief single exposures to hydrogen fluoride. Am. Ind. Hyg. Assoc. J. 24: 253-261.

Safe Drinking Water Committee. (1977) Drinking water and health. Washington, DC: National Academy of Sciences; pp. 369-400, 433-435.

Safe Drinking Water Committee. (1980) Drinking water and health: v. 3. Washington, DC: National Academy Press; pp. 279-283, 363.

Sax, N. I. (1984) Dangerous properties of industrial materials. 6th ed. New York, NY: Van Nostrand Reinhold Company; pp. 1427-1428, 1548-1549, 2430-2431.

Schmidt, C. W. (1983) Neighborhood fluorosis with skeletal manifestations. Fluoride 16: 83-90.

Shepard, T. H. (1983) Catalog of teratogenic agents. 4th ed. Baltimore, MD: The Johns Hopkins University Press; pp. 196-197.

Shupe, J. L.; Miner, M. L.; Greenwood, D. A.; Harris, L. E.; Stoddard, G. E. (1963) The effects of fluorine on dairy cattle: II. clinical and pathologic effects. Am. J. Vet. Res. 24: 964-979.

Sittig, M. (1985) Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications; pp. 456-459, 508-509, 799.

Skare, J. A.; Schrotel, K. R.; Nixon, G. A. (1986a) Lack of DNA-strand breaks in rat testicular cells after in vivo treatment with sodium fluoride. Mutat. Res. 170: 85-92.

Skare, J. A.; Wong, T. K.; Evans, B. L. B.; Cody, D. B. (1986b) DNA-repair studies with sodium fluoride: comparative evaluation using density gradient ultracentrifugation and autoradiography. Mutat. Res. 172: 77-87.

Smith, G. E. (1986a) Fluoride, immunity and tooth decay [letter]. Nature (London) 323: 198.

Smith, G. E. (1986b) Fluoride, the environment, and human health. Perspect. Biol. Med. 29: 560-572.

Smith, G. E. (1986c) Can a vaccine prevent cavities? Trends Pharmacol. Sci. 8: 108-112.

Smith, F. A.; Hodge, H. C. (1979) Airborne fluorides and man: part I. Crit. Rev. Environ. Control 8: 293-371.

Smith, F. A.; Hodge, H. C.; MacGregor, J. T. (1982) Fluoride in pregnancy. In: Milunsky, A.; Friedman, E. A.; Gluck, L., eds. Advances in perinatal medicine: v. 2. New York, NY: Plenum Publishing Corporation; pp. 1-46.

Snow, G. R.; Anderson, C. (1986) Short-term chronic fluoride administration and trabecular bone remodeling in beagles: a pilot study. Calcif. Tissue Int. 38: 217-221.

Spencer, H.; Kramer, L.; Osis, D.; Wiatrowski, E.; Norris, C.; Lender, M. (1980) Effect of calcium, phosphorus, magnesium, and aluminum on fluoride metabolism in man. In: Levander, O. A.; Cheng, L., eds. Micronutrient interactions: vitamins, minerals, and hazardous elements. Ann. N. Y. Acad. Sci. 355: 181-194.

Spira, L. (1944) Incidence of dystrophies caused by fluorine in organs regulated by the parathyroid glands. J. Hyg. 43: 402-408.

SRI International. (1985) CEH manual of current indicators - supplemental data. In: Chemical economics handbook. Menlo Park, CA: SRI International; pp. 294-297.

Stokinger, H. E. (1949) Toxicity following inhalation of fluorine and hydrogen fluoride. In: Voegtlin, C.; Hodge, H. C., eds. Pharmacology and toxicology of uranium compounds. New York, NY: McGraw-Hill Book Company, Inc.; pp. 1021-1057.

Stokinger, H. E. (1981) The halogens and the nonmetals boron and silicon: 1. halogens: 1.2. fluorine, F_2. In: Clayton, G. D.; Clayton, F. E., eds. Patty's industrial hygiene and toxicology: v. 2B, toxicology. 3rd ed. New York, NY: John Wiley & Sons; pp. 2937-2954.

Stuewe, A. H. (1958) Hydrogen fluoride...where it goes, how it's made, why it's growing. Chem. Eng. News 36: 34-38, 57.

Sutton, P. R. N. (1986) Lung cancer: is fluoride in cigarette smoke an etiological factor? Med. Hypotheses 20: 51.

Temple, P. J.; Weinstein, L. H. (1978) Is hydrogen fluoride mutagenic in plants? J. Air Pollut. Control Assoc. 28: 151-152.

Tepperman, P. B. (1980) Fatality due to acute systemic fluoride poisoning following a hydrofluoric acid skin burn. JOM J. Occup. Med. 22: 691-692.

Trevino, M. A.; Herrmann, G. H.; Sprout, W. L. (1983) Treatment of severe hydrofluoric acid exposures. JOM J. Occup. Med. 25: 861-863.

Tsutsui, T.; Suzuki, N.; Ohmori, M.; Maizumi, H (1984a) Cytotoxicity, chromosome aberrations and unscheduled DNA synthesis in cultured human diploid fibroblasts induced by sodium fluoride. Mutat. Res. 139: 193-198.

Tsutsui, T.; Ide, K.; Maizumi, H. (1984b) Induction of unscheduled DNA synthesis in cultured human oral keratinocytes by sodium fluoride. Mutat. Res. 140: 43-48.

Tsutsui, T.; Suzuki, N.; Ohmori, M. (1984c) Sodium fluoride-induced morphological and neoplastic transformation, chromosome aberrations, sister chromatid exchanges, and unscheduled DNA synthesis in cultured Syrian hamster embryo cells. Cancer Res. 44: 938-941.

U.S. Environmental Protection Agency. (1977) Compilation of air pollutant emission factors. 3rd ed. (including supplements 1-7). Research Triangle Park, NC: Office of Air Quality Planning and Standards; sects. 5.8, 6.10, 7.5, 8.12, 9.1; report no. AP-42. Available from: GPO, Washington, DC; S/N 055-003-00087-4.

U.S. Environmental Protection Agency. (1980a) Supplement no. 10 for compilation of air pollutant emission factors. 3rd ed. Research Triangle Park, NC:

Office of Air Quality Planning and Standards; sect. 5.8; report no. AP-42-SUPPL-10. Available from: NTIS, Springfield, VA; PB82-232190.

U.S. Environmental Protection Agency. (1980b) Supplement no. 11 for compilation of air pollutant emission factors. 3rd ed. Research Triangle Park, NC: Office of Air Quality Planning and Standards; sects. 5.8, 6.10, 7.5; report no. AP-42-SUPPL-11. Available from: NTIS, Springfield, VA; PB81-178014.

U.S. Environmental Protection Agency. (1983) Supplement no. 14 for compilation of air pollutant emission factors. 3rd ed. Research Triangle Park, NC: Office of Air Quality Planning and Standards; sect. 7.5; report no. AP-42-SUPPL-14. Available from: NTIS, Springfield, VA; PB83-250720.

U.S. Environmental Protection Agency. (1984) Supplement no. 15 for compilation of air pollutant emission factors. 3rd ed. Research Triangle Park, NC: Office of Air Quality Planning and Standards; sect. 7.1; report no. AP-42-SUPPL-15. Available from: NTIS, Springfield, VA; PB84-199744.

U.S. Environmental Protection Agency. (1986) Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Fluoride Online. (Verification date 6-30-88). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

van Haut, H.; Krause, G. H. M. (1982) Wirkungen von Fluorwasserstoff-Immissionen auf die Vegatation [Effects of hydrogen fluoride emissions on vegetation]. LIS-Ber. (25).

Vernot, E. H.; MacEwen, J. D.; Haun, C. C.; Kinkead, E. R. (1977) Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42: 417-423.

Voroshilin, S. I.; Plotko, E. G.; Gatiyatullina, E. Z.; Gileva, E. A. (1973) Cytogenetic effect of inorganic fluorine compounds on human and animal cells in vivo and in vitro. Sov. Genet. (Engl. Transl.) 9: 492-496.

Voroshilin, S. I.; Plotko, E. G.; Nikiforova, V. Ya. (1975) Mutagenic effect of hydrogen chloride on animals. Cytol Genet. (Engl. Transl.) 9: 40-42.

Waldbott, G. L. (1961) "The physiologic and hygienic aspects of the absorption of inorganic fluorides" -- comments on the symposium. Arch. Environ. Health 2: 155-167.

Waldbott, G. L. (1973) Health effects of environmental pollutants. St. Louis, MO: The C. V. Mosby Company; pp. 150-168.

Waldbott, G. L. (1980) Fluoridation: a clinician's experience. South. Med. J. 73: 301-306.

Waldbott, G. L. (1981) Mass intoxication from accidental overfluoridation of drinking water. Clin. Toxicol. 18: 531-541.

Waldbott, G. L.; Lee, J. R. (1978) Toxicity from repeated low-grade exposure to hydrogen fluoride--case report. Clin. Toxicol. 13: 391-402.

Watanabe, M.; Yoshida, Y.; Watanabe, M.; Shimada, M.; Kurimoto, K.; Kihara, T. (1975) Effects of hydrofluoric acid on glucose metabolism of the mouse studied by whole-body autoradiography. Br. J. Ind. Med. 32: 316-320.

Weast, R. C.; Astle, M. J.; Beyer, W. H., eds. (1986) CRC handbook of chemistry and physics: a ready-reference book of chemical and physical data. 67th ed. Boca Raton, FL: CRC Press, Inc.; pp. B-91, B-94, B-130, D-121-D-122, D-163, D-193.

Weiss, G., ed. (1980) Hazardous chemicals data book. Park Ridge, NJ: Noyes Data Corporation; pp. 473, 511, 515, 822.

White, D. A. (1980) Hydrofluoric acid--a chronic poisoning effect. J. Soc. Occup. Med. 30: 12-14.

Whitford, G. M.; Pashley, D. H. (1984) Fluoride absorption: the influence of gastric acidity. Calcif. Tissue Int. 36: 302-307.

Whitford, G. M.; Pashley, D. H.; Stringer, G. I. (1976) Fluoride renal clearance: a pH-dependent event. Am. J. Physiol. 230: 527-532.

Whitford, G. M.; Reynolds, K. E.; Pashley, D. H. (1979) Acute fluoride toxicity: influence of metabolic alkalosis. Toxicol. Appl. Pharmacol. 50: 31-39.

Williams, C. R. (1942) Atmospheric contamination from the casting of magnesium. J. Ind. Hyg. Toxicol. 24: 277-280.

Windholz, M.; Budavari, S.; Blumetti, R. F.; Otterbein, E. S., eds. (1983) The Merck index. 10th ed. Rahway, NJ: Merck & Co., Inc.; pp. 230, 596, 695-696, 1235.

World Health Organization. (1984) Fluorine and fluorides. Geneva, Switzerland: World Health Organization. (Environmental health criteria: 36).

Yolken, R.; Konecny, P.; McCarthy, P. (1976) Acute fluoride poisoning. Pediatrics 58: 90-93.

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